



OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

RECEIPT OF DOCUMENTS FROM REBECCA CALDERONE

On May 12, 2005, SA DAVID L. COTNER, Special Investigations Unit, received documents from Dr. REBECCA CALDERONE (919/966-0617), Director, Human Studies Division (HSD), EPA at the University of North Carolina (UNC) in her office, room number 152, at the EPA Human Studies Building, 104 Mason Farm Road, Chapel Hill, NC. CALDERONE was not shown identification as she was previously known to reporting agent. The purpose of the receipt of documents was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

The documents received from CALDERONE included two reports submitted by Dr. FRED MILLER. The first was titled IRB# 91-EPA-226 Determination of Deposition Dose of Inhaled Particles in Human Lungs, Review of Expected Mass Deposited and Potential Risk to Subjects, dated September 11, 2001 (Attachment 1). The second was titled Assessment of Potential Maximum Dose in ADEPOSIT Subjects, dated March 15, 2002 (Attachment 2). CALDERONE also provided a copy of the Annual Update on HSD Human Subjects Progressive Action Plan, dated July 9, 2004 (Attachment 3).

CALDERONE provided a memorandum dated April 4, 2002 from Dr. ROBERT DEVLIN, titled Exposure of Subjects to Sebacate Particles in ADEPOSIT (Attachment 4). The memorandum referred to a study by P. Brand, et. al, titled Total Deposition of Therapeutic Particles During Spontaneous and Controlled Inhalations (Attachment 5). The memorandum summarized the Brand study and stated the Brand paper had subjects who 'were exposed to a particle concentration of 260 mg/m(cubed) and there were no reported adverse health effects associated with the study. Dr. Kim's subjects were exposed to a maximum particle concentration of 150 mg/m (cubed) with no reported adverse health effects. Assuming subjects in both studies were using the same breathing pattern, Dr. Kim's subjects inhaled only 58% as much particle mass as the subjects in the Brand study.'

Calderone also provided two memorandums given to Dr. CHONG KIM which ultimately gave

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Conducted by: SA David L. Cotner	OI File No: 2005-0002
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him a seven day suspension. A Notice of Proposed Suspension, dated October 3, 2001 (Attachment 6) from Dr. LINDA BIRNBAUM proposed a 21-day suspension of KIM. A Notice of Decision to Suspend, dated November 6, 2001 (Attachment 7) from Dr. HAROLD ZENICK suspended KIM for seven days from January 2 - January 8, 2002. The memorandum also referred to a September 24, 2001 memorandum from BIRNBAUM to KIM that indefinitely banned KIM from conducting human studies.

Attachments

1. Review of Expected Mass Deposited & Potential Risk to Subjects, dated September 11, 2001
2. Assessment of Potential Maximum Dose in ADEPOSIT Subjects, dated March 15, 2002
3. Annual Update on HSD Human Subjects Progressive Action Plan, dated July 9, 2004
4. Memorandum dated April 4, 2002 from Dr. ROBERT DEVLIN
5. Study by P. Brand, et. al, titled Total Deposition of Therapeutic Particles During Spontaneous and Controlled Inhalations
6. Notice of Proposed Suspension, dated October 3, 2001
7. Notice of Decision to Suspend, dated November 6, 2001

CONFIDENTIAL

IRB# 91-EPA-226 Determination of Deposition Dose
of Inhaled Particles in Human Lungs

Review of Expected Mass Deposited
and
Potential for Risk to Subjects

Submitted to

Dr. Linda S. Birnbaum
Director, Human Studies Division
U.S. Environmental Protection Agency
Chapel Hill, NC 27599

Submitted by

Dr. Frederick J. Miller
CIIT Centers for Health Research
Research Triangle Park, NC 27709

Dr. Bahman Asgharian
CIIT Centers for Health Research
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September 11, 2001

Attachment (1)

Nature of the Deposition Studies

The protocol covered by IRB# 91-EPA-226 provides for exposing human subjects to di(2-ethylhexyl) sebacate (DEHS) under varying conditions of particle size, breaths per minute, airflow rate, particle concentration, and aerosol dispersity (mono- vs. polydisperse). Two types of exposure regimens are being studied, one involving a bolus delivery of the aerosol and the other with non-bolus delivery. The protocol indicates that five different groups of people will be studied. These include young normals (age = 18–40 yrs), old normals (age > 60 yrs), cigarette smokers (age = 18–40 yrs), asthmatics (age = 18–40 yrs), and COPD patients (age > 40 yrs). The protocol notes that the polydisperse aerosol exposure regimen will be restricted to 20 young normal subjects. Otherwise, all age groups are to be studied for the various combinations of breathing frequency, particle size, and flow rates. Gender is being examined indirectly in that male and female subjects are being recruited.

The Charge

The protocol states that the actual total lung dose of DEHS particles is expected to be < 50 µg. The accuracy of this statement has been called into question. We were asked to review the protocol and calculate expected lung deposition. Further, we were asked to comment on the potential for risk to subjects in the various study groups if the predicted dose was found to be significantly greater than that stated in the protocol.

Comments on the Protocol

While we were asked to review the protocol and focus on computations that would evaluate the correctness of the statement in the protocol that a subject would receive 50 µg of DEHS per day of exposure, there are several aspects of the protocol that should be made more explicit. In addition, there are inconsistencies within the protocol that need to be corrected. For example, on the selection criteria for asthmatics, the statement is made that "the same as normal criteria above for the first five criteria are to be applied to asthmatics." Yet the fourth criteria for normals is that the individual not have a personal history of hay fever or asthma. Obviously this criteria can not be met and still have the individual be studied in a group of asthmatics.

The protocol is vague in several areas that relate to being able to ascertain the exact experimental design that was used. For example, the statement is included in the protocol "Lung deposition measurement will be repeated for three (1, 3, and 5 µm diameter for ADEPOSIT), or four (0.04, 0.06, 0.08, and 0.1 µm diameter for SDEPOSIT) different size particles, each size on separate day. ADEPOSIT and SDEPOSIT will be conducted in parallel and independently, and

the same subjects will be encouraged to participate in both studies. For polydisperse aerosols (POLYDEPO), lung deposition will be measured for six different size aerosols on the same day. Subjects will make two visits to complete the study." One can not tell from this statement if, for example, in the polydisperse protocol does Visit 1 include all particle sizes and σ_g s for the fixed tidal volume of 500 ml or does it include all particle sizes and tidal volumes for a fixed σ_g ? The way the protocol is written there is no way to discern which was done.

Dosimetry Model Used for Calculations

There are a number of anatomical models of the human lung available in the literature. The model of Weibel (1963) is a typical path lung model based upon some measurements and some extrapolations of calculated values. A typical path model based upon more extensive measurements of the human lung was developed by Yeh and Schum (1980). Yeh and Schum also developed a typical path lobar-specific model for humans. The detailed lung cast measurements of the human lung made by Raabe and coworkers (1976) have been used by Hofmann, Koblinger and colleagues to develop stochastic lung models (Koblinger and Hofmann, 1985, 1988, 1990; Hofmann and Koblinger, 1990, 1992). In the stochastic modeling of lung deposition, Monte Carlo methods are employed that exploit the statistical distributions of the morphometric data on diameters, lengths, branching and gravity angles for individual airway generations, as well as correlations between daughter and parent airways in major and minor daughter airways. The human model used for the deposition computations presented in this review are based upon the recently published stochastic, multiple-path model of the human lung developed by Asgharian et al. (2001). This model is the most advanced dosimetry model currently available for calculating deposition in specific lobes and individual paths and makes the most extensive use of available biological and statistical data on lung geometry. Since there are toxicological data available on DEHS from a rat inhalation study, computations were also made for the delivered dose to rats of DEHS. For these calculations, the multiple path model of particle deposition in the rat lung of Anjilvel and Asgharian (1995) was used.

Assumptions for Worst Case Calculations

The lack of specificity in the protocol required us to invoke the following assumptions:

- For ultrafine particles, all concentrations were assumed to be derived from 80,000 particles per cm^3 .

- For the fine and coarse mode particles, a number concentration of 10,000 particles per cm^3 was used for both the 3- and 5- μm diameter particles, while 50,000 particles per cm^3 was used for the 1- μm particle calculations.
- All calculations were made assuming 20 breaths for a given combination of breathing frequency, flow rate, tidal volume, and particle size.

Monodisperse Aerosol Exposures

With monodisperse aerosols, the protocol calls for both an aerosol bolus and a nonbolus exposure. Since nonbolus exposures will yield the highest delivered dose, only calculations for the nonbolus aerosol exposure to monodisperse aerosols of various particle sizes were computed. Since the potential effects of a particle on the lung vary by anatomical region, calculations are presented separately for the tracheobronchial (TB) and the pulmonary (P) regions. Thoracic region deposition is represented by the sum of the TB and P deposition. While a subsequent section examines the potential toxicological implications for various groups of subjects, the deposition calculations needed for such an analysis must be separated by region. Since the subjects studied were of varying body weight, height, and lung volume, the stochastic lung model allows one to study deposition in small lungs compared to large lungs. By doing so, the average deposition across the study subjects was likely captured.

As noted earlier, the protocol wording is ambiguous for the monodisperse aerosol studies as to which particle sizes were done on a given day. The vagueness of the wording by using the term "each size on separate day" could vary from a subject returning on seven different occasions or more likely returning on two different occasions. The calculations presented are for returning on two separate occasions, one for aerosol exposures to the fine particles and the other for exposure to ultrafine particles. Once again, if this was not the way the actual study was conducted, the deposition data presented in this section will need to be recombined to construct the estimate of delivered dose. Since particle concentrations are not given in the protocol and were not available to us, we made worst case exposure concentration assumptions for characterization of potential risk.

In the event that EPA officials wish to make more refined calculations for delivered dose by using actual number concentrations that should be reported in the investigator's laboratory notebook, Tables 1 and 2 are provided. In these tables, the deposition fraction for TB and P deposition in small and large stochastically generated lungs are given for the particle sizes and tidal volumes used.

Using the worst case assumptions described earlier, Tables 3 and 4 provide the calculated delivered dose of DEHS for the monodisperse aerosol exposure studies. As can be seen from Table 3, the ultrafine particulate studies result in a negligible mass deposited in the TB region (0.895 to 1.07 μg) and in the P region (1.51 to 2.27 μg), even if all of the particle sizes and tidal volumes were studied on the same day. As Table 4 demonstrates, negligible deposition in the tracheobronchial and pulmonary regions also occurs for the 1- μm diameter DEHS particle. For this particle size, TB deposition in small and large lungs ranges from about 241–246 μg while pulmonary deposition ranges from 277–523 μg . Moreover, these burdens arise if all exposure scenarios involving 1- μm particles were conducted on the same day.

The same can not be said for the coarse mode particles studied. Depending upon the specific breathing frequency, tidal volume, and particle size (3 μm or 5 μm) used in a given exposure, tracheobronchial deposition can vary from about 0.15 mg to more than 6 mg while pulmonary deposition varies between 0.057 mg and 6.79 mg (see Table 4). It is important to note that these calculations arise from using the worst case assumptions stated earlier. After a quality assurance (QA) audit of the raw data, a table can be constructed for the exact number of breaths each subject used in a particular exposure combination, the number of particle sizes and tidal volumes administered on a given day, and the time interval between potential return visits. Given this information more accurate estimates of dose can be calculated using deposition fractions in Tables 1 and 2 and other pertinent information. Alternatively, the deposition mass can be adjusted by division of the product of any factors that were overestimated (e.g., if 10 breaths were used then the deposition masses appearing in our tables would need to be divided by 2; if the number of particles per cm^3 are less than those that were assumed for these calculations, then the deposition mass can be altered by the ratio of the assumed to the actual number).

If the eight combinations of breathing frequency and tidal volume were all studied on the same day, the mass of 5- μm particles deposited in the TB region would range from 20.3–22.4 mg. Pulmonary region deposited mass would range from about 15–25 mg. We feel certain that fewer breaths than 20 were used by most subjects and that the number concentration was probably not 10,000 particles per cm^3 as stated in the protocol, both of which would drastically reduce the deposited mass of DEHS particles. *Our reason for feeling that actual exposures may have been much less stems from a sentence in supplemental information we received after we had made our calculations. In a memo from Dr. Chong Kim to Dr. Linda Birnbaum dated August 20, 2001, the following statement is made "...During the test, they used a portable aerosol*

monitor...and noticed the mass reading on the DRAM was about $10\text{mg}/\text{m}^3$ for $5\text{-}\mu\text{m}$ diameter particles." If this statement is correct, then only 166 particles per cm^3 of $5\text{-}\mu\text{m}$ DEHS particles was used for exposures compared to the 10,000 particles per cm^3 stated in the protocol and so our calculations of deposited mass would need to be divided by 60. But even the above sentence in the memo is internally inconsistent with another sentence in the memo that states "...and realized that the calculated lung dose (about 1.5 mg) indeed would be..." Using 166 particles per cm^3 would result in thoracic doses between 0.6–0.8 mg and pulmonary doses between 0.25–0.42 mg based upon the calculations we give in Table 4. Simply put, there is no way the information in the protocol can be used to discern what correction should be made to our worst case calculations.

Polydisperse Aerosol Studies

The exact nature of how the exposure scenarios were conducted (i.e., how many, particle size, tidal volume, etc. combinations were done on a given day) is not evident from the protocol. The most likely scenario was to get the generator producing at a fixed σ_g and then to ask subjects to breathe first at a tidal volume of 500 ml and then later in the day breathe at a tidal volume of 1000 ml. Thus, the calculations presented here are based upon this assumption. If this proves to be incorrect, then various parts of the tables will need to be combined to obtain a more accurate prediction of estimated delivered dose of DEHS.

Table 5 gives the deposition fractions for the polydisperse aerosols for the 0.1, 1, and $3\text{-}\mu\text{m}$ particles that were studied at tidal volumes of 500 and 1000 ml. The corresponding deposited mass of DEHS particles for the TB and P regions is given in Table 6. If indeed all particle sizes and tidal volumes for a given σ_g were studied on the same day, then Table 6 shows that the TB deposited mass ranged from about 0.7 mg to 1.15 mg, while P deposited mass ranged from about 0.72 mg to 1.35 mg. A QA audit needs to be conducted to reconstruct the exact combination of exposure scenarios that a given subject participated in and then the data in Tables 5 and 6 can be used as described earlier to obtain the correct estimate of delivered dose.

Toxicity of DEHS

DEHS is a straight-chain diester that has been used in numerous deposition studies involving human subjects. Most toxicity studies in animals have used instillation of DEHS. In a 1996 study, Brain and colleagues intratracheally instilled DEHS in hamsters to examine potential

acute lung injury. These investigators found that a dose of 3.75-mg DEHS/100 g body weight caused negligible acute pulmonary toxicity. In the discussion section of the Brain et al. study, they compared the toxicity they saw with equivalent high doses of metal oxides. The metal oxides produce significant changes in some of the parameters that were measured, but DEHS produced minimal changes. Far lower doses of toxic materials produce effects on PMNs and other end points that are greater than DEHS causes by a factor of around 40. Among the animal toxicological studies, the study by Rubin et al. (1983), which was presented at the annual meeting of the Society of Toxicology but never published in a journal, stands out because these investigators used an inhalation model. Rats were exposed to DEHS aerosol (0.9- μ m mass median diameter) at exposure doses up to 250 mg/m³ for four hours per day, five days per week for seven weeks. Using the multiple-path dosimetry model of Anjilvel and Asgharian (1995) for the rat, we modeled the deposition and clearance of DEHS associated with the Rubin et al. (1983) study. At the end of the first week of exposure, the alveolar mass retained was about 17 mg. Over the 7-week exposure period, the alveolar mass rose to approximately 20 mg. TB mass retention never exceeded 0.048 mg during the course of the study. In their study, Rubin and colleagues noted only slight changes in the lung pressure-volume curve, and there were no alterations in pulmonary macrophage or liver function. Thus, while 250 mg/m³ is an astronomically high level of exposure, the resultant toxicity was minimal. Based on studies using healthy hamsters and rats, one may infer that DEHS is of minimal toxicity to healthy subjects even at high exposure levels.

Potential Risk to Human Subjects Studied in IRB# 91-EPA-226

While there is no question that the human subjects involved in this study had deposited masses in the pulmonary and tracheobronchial regions far greater than the 50 μ g stated in the protocol, the real issue is how high was the deposited dose and was there an associated potential risk. To answer this question, we need to examine potential consequences for each of the five study groups.

Two of the five groups studied were classified as "young normals" and "old normals." From the toxicity data and the relative comparison of dose between animals and humans, it is very unlikely that doses on the order of several milligrams would provide any toxicity to healthy subjects. This point is articulated well in the discussion section of the Brain et al. (1996) paper, where the authors note that the dose they used in their hamster studies would be the equivalent to 37.5 mg/kg. Given the average body weight of 50–70 kg in female and male human subjects, respectively, an extremely large deposited mass would have minimal risk for acute toxicity.

Thus, the milligram quantities likely deposited in normal subjects still should not be associated with any risk.

The category of smokers is difficult to assess relative to whether or not any potential risk might have been involved. Smokers typically have greater deposits of particles than normal subjects. However, since the protocol merely classifies the subjects as smokers, there is no indication that the smoking status was associated with a frank disease state at the time they were exposed to DEHS. Thus, the most likely scenario would be that the smokers had no greater risk than normal subjects.

The cause for concern for potential risk resulting from the inhalation exposures that were used in the DEHS deposition studies centers on asthmatics and individuals with COPD. Not knowing the exact concentration for the exposure, it is difficult to determine the potential risk for these two categories of subjects. Given the epidemiological data associated with PM10 for both asthmatics and individuals with COPD, the issue of potential risk follows a different course for the two groups. For asthmatics, the mass deposited and the exposure levels used in the study may have had the potential for exacerbation of the individual's asthma condition. This statement is made in recognition of the relatively far smaller exposure levels with PM10 that have been associated with increased medication use of asthma and hospital admissions for asthma. On the other hand, given the acute nature of the response coupled with the fact that there was no indication that any of the asthmatic subjects had any difficulties with the DEHS inhalation exposures, one of two scenarios would be operative: (1) in view of the minimal toxicity of DEHS particles, the exacerbation of asthma is indeed not present with the DEHS levels used in this study or (2) the potential was there for an adverse response but the lesser severity of asthma of the subjects used coupled with the probability of an event occurring were such that the EPA investigator "dodged a bullet."

Of the five groups of subjects studied, our opinion is that individuals with COPD would be the group of greatest concern for potential risk. The PM10 literature is replete with studies demonstrating acute mortality and morbidity in subjects with COPD. Moreover, the exposure levels involved for these effects are drastically lower than those used in the EPA dosimetry studies, albeit the EPA exposures were of a very short duration. For example, to receive the same pulmonary dose of 5- μ m particles over a 24-hr period as was potentially administered in the deposition study, a person would need to be exposed to at least 40 mg/m³, an exposure level more than 2 orders of magnitude above the PM10 standard (at least before the courts recently struck down the EPA's PM10 standard).

Not only do COPD individuals have increased deposition relative to normal subjects, their ability to clear particles is relatively poor. Thus, even if acute responses were not invoked, one can not categorically rule out, depending upon the actual doses delivered, that COPD individuals may have had potential for adverse responses subsequent to their participation in the studies.

We would strongly suggest that a small, independent group (perhaps one person each from the areas of epidemiology, clinical pulmonary, and dosimetry modeling) be brought in to examine the potential for risk in the various subjects used in this study after it has been clearly established what the actual doses received by the subjects were. While our inference must be speculative due to the protocol not containing enough specifics to calculate accurately the dose of DEHS deposited, the presence of a tolerance distribution in the human population allows for the potential for some responses in more sensitive individuals. While DEHS has been used in deposition studies, the magnitude and number of exposures were small compared to those that could be calculated from the numbers presented in the protocol. The real issues remains clearly establishing what the actual exposures were and then having an assessment of the potential for risk and making modifications to any future protocols that ensure lower DEHS exposure levels are used.

Recommended Path Forward

- Conduct a QA audit of the study records to establish the following information for each subject.
 - The exact nature of the exposure combinations (i.e., what particle sizes, flow rates, tidal volumes) done on a given day and the number of breaths the subject took for each exposure combination.
 - The interval of time between daily visits if the subject participated in more than one study (ADEPOSIT, SDEPOSIT, POLYDEPO) or returned on separate occasions in any given study.
- The QA audit should at a minimum focus on all persons exposed to 3- μ m or 5- μ m monodisperse particles in the nonbolus regimen. The next priority would be an audit of the records for persons exposed to the 3- μ m aerosol in the POLYDEPO study.
- Once the complete exposure scenario information is tabulated for subjects, calculate the predicted mass of DEHS particles deposited in the TB and P regions for each exposure scenario and add them together if more than one scenario was used for a subject on a given day.

- For individuals having more than one visit, compute the net mass retained in the TB and P regions after the last visit by the subject. This requires using a clearance model and knowing the time interval between days of exposure.
- Clarify via amendments to protocol IRB #91-EPA-226 more accurate estimates of what the deposited dose of DEHS is expected to be. Note: Whatever the calculations show was the mass delivered in subjects thus far, the total mass deposited should be reduced in any subsequent studies to be less than 1–2 mg in normal subjects and less than 0.5 mg in asthmatics or in individuals with COPD. *
- Have a team of scientists review the deposition data from this study relative to deposited doses in other published human studies and identify what would be an acceptable range of deposited mass in the TB and P regions for various sized DEHS particles.
- Armed with calculations of likely deposited mass for subjects studied thus far, have an independent review committee evaluate any potential risks that may have ensued from the exposures that were used.
- Notify study participants that they had higher deposited masses of DEHS particles than specified in the protocol and make them aware of any potential health risks identified by an independent review committee.
- Ensure all future protocols are *a priori* peer reviewed and that an experimental design table is included that easily lets a reviewer follow what is to be done to each subject in the study.

Table 1. Monodisperse Particle Exposures: Ultrafine Deposition Fractions

Particle Characteristics		Breathing Parameters		Deposition Fraction			
Diameter (μm)	σ_g	BF	Tidal Vol. (ml)	(Small Lung)		(Large Lung)	
				TB	P	TB	P
0.04	1	7.5	500	0.189	0.439	0.229	0.152
0.04	1	15	500	0.15	0.384	0.179	0.136
0.04	1	30	500	0.125	0.309	0.145	0.110
0.04	1	60	500	0.113	0.232	0.125	0.083
0.04	1	3.75	1000	0.201	0.539	0.273	0.340
0.04	1	7.5	1000	0.158	0.486	0.211	0.334
0.04	1	15	1000	0.132	0.402	0.169	0.295
0.04	1	30	1000	0.118	0.309	0.144	0.238
0.06	1	7.5	500	0.14	0.381	0.169	0.135
0.06	1	15	500	0.114	0.305	0.134	0.109
0.06	1	30	500	0.101	0.229	0.113	0.082
0.06	1	60	500	0.096	0.163	0.103	0.059
0.06	1	3.75	1000	0.148	0.484	0.200	0.335
0.06	1	7.5	1000	0.121	0.398	0.158	0.294
0.06	1	15	1000	0.106	0.305	0.131	0.236

0.06	1	30	1000	0.101	0.221	0.118	0.177
0.08	1	7.5	500	0.116	0.323	0.137	0.117
0.08	1	15	500	0.098	0.245	0.112	0.089
0.08	1	30	500	0.089	0.177	0.097	0.065
0.08	1	60	500	0.089	0.123	0.092	0.045
0.08	1	3.75	1000	0.122	0.417	0.162	0.308
0.08	1	7.5	1000	0.103	0.323	0.131	0.253
0.08	1	15	1000	0.094	0.236	0.112	0.193
0.08	1	30	1000	0.093	0.166	0.105	0.140
0.1	1	7.5	500	0.100	0.279	0.118	0.101
0.1	1	15	500	0.087	0.205	0.098	0.075
0.1	1	30	500	0.082	0.144	0.088	0.053
0.1	1	60	500	0.084	0.099	0.086	0.036
0.1	1	3.75	1000	0.106	0.364	0.139	0.279
0.1	1	7.5	1000	0.092	0.272	0.114	0.220
0.1	1	15	1000	0.086	0.194	0.101	0.162
0.1	1	30	1000	0.088	0.134	0.097	0.115

Table 2. Monodisperse Particle Exposures: Fine and Coarse Deposition Fractions

Particle Characteristics		Breathing Parameters		Deposition Fraction			
Diameter (μm)	σ_g	BF	Tidal Vol. (ml)	(Small Lung)		(Large Lung)	
				TB	P	TB	P
1	1	7.5	500	0.061	0.160	0.076	0.060
1	1	15	500	0.061	0.095	0.067	0.035
1	1	30	500	0.067	0.056	0.067	0.020
1	1	60	500	0.081	0.034	0.075	0.012
1	1	3.75	1000	0.065	0.227	0.089	0.210
1	1	7.5	1000	0.118	0.474	0.076	0.132
1	1	15	1000	0.070	0.080	0.074	0.079
1	1	30	1000	0.083	0.048	0.081	0.046
3	1	7.5	500	0.129	0.455	0.210	0.160
3	1	15	500	0.107	0.337	0.146	0.125
3	1	30	500	0.132	0.224	0.117	0.080
3	1	60	500	0.270	0.113	0.122	0.046
3	1	3.75	1000	0.148	0.581	0.256	0.358
3	1	7.5	1000	0.118	0.474	0.173	0.346
3	1	15	1000	0.133	0.315	0.134	0.269
3	1	30	1000	0.259	0.165	0.133	0.173
5	1	7.5	500	0.249	0.480	0.388	0.135

5	1	15	500	0.204	0.453	0.268	0.161
5	1	30	500	0.326	0.293	0.209	0.136
5	1	60	500	0.721	0.070	0.263	0.083
5	1	3.75	1000	0.270	0.562	0.480	0.239
5	1	7.5	1000	0.212	0.558	0.326	0.330
5	1	15	1000	0.314	0.397	0.241	0.343
5	1	30	1000	0.708	0.111	0.271	0.261

Table 3. Monodisperse Particle Exposures: Ultrafine Deposited Mass

Particle Characteristics		Breathing Parameters		Deposition (mg)			
Diameter (μm)	σ_g	BF	Tidal Vol. (ml)	(Small Lung)		(Large Lung)	
				TB	P	TB	P
0.04	1	7.5	500	5.07E-06	1.18E-05	6.14E-06	4.07E-06
0.04	1	15	500	4.02E-06	1.03E-05	4.80E-06	3.65E-06
0.04	1	30	500	3.35E-06	8.28E-06	3.89E-06	2.95E-06
0.04	1	60	500	3.03E-06	6.22E-06	3.35E-06	2.23E-06
0.04	1	3.75	1000	1.08E-05	2.89E-05	1.46E-05	1.82E-05
0.04	1	7.5	1000	8.47E-06	2.61E-05	1.13E-05	1.79E-05
0.04	1	15	1000	7.08E-06	2.16E-05	9.06E-06	1.58E-05
0.04	1	30	1000	6.33E-06	1.66E-05	7.72E-06	1.28E-05
0.06	1	7.5	500	1.27E-05	3.45E-05	1.53E-05	1.22E-05
0.06	1	15	500	1.03E-05	2.76E-05	1.21E-05	9.86E-06
0.06	1	30	500	9.14E-06	2.07E-05	1.02E-05	7.42E-06
0.06	1	60	500	8.69E-06	1.47E-05	9.32E-06	5.34E-06
0.06	1	3.75	1000	2.68E-05	8.76E-05	3.62E-05	6.06E-05
0.06	1	7.5	1000	2.19E-05	7.20E-05	2.86E-05	5.32E-05
0.06	1	15	1000	1.92E-05	5.52E-05	2.37E-05	4.27E-05
0.06	1	30	1000	1.83E-05	4.00E-05	2.14E-05	3.20E-05
0.08	1	7.5	500	2.49E-05	6.93E-05	2.94E-05	2.51E-05
0.08	1	15	500	2.10E-05	5.25E-05	2.40E-05	1.91E-05

0.08	1	30	500	1.91E-05	3.80E-05	2.08E-05	1.39E-05
0.08	1	60	500	1.91E-05	2.64E-05	1.97E-05	9.65E-06
0.08	1	3.75	1000	5.23E-05	1.79E-04	6.95E-05	1.32E-04
0.08	1	7.5	1000	4.42E-05	1.39E-04	5.62E-05	1.09E-04
0.08	1	15	1000	4.03E-05	1.01E-04	4.80E-05	8.28E-05
0.08	1	30	1000	3.99E-05	7.12E-05	4.50E-05	6.01E-05
0.1	1	7.5	500	4.19E-05	1.17E-04	4.94E-05	4.23E-05
0.1	1	15	500	3.64E-05	8.59E-05	4.11E-05	3.14E-05
0.1	1	30	500	3.43E-05	6.03E-05	3.69E-05	2.22E-05
0.1	1	60	500	3.52E-05	4.15E-05	3.60E-05	1.51E-05
0.1	1	3.75	1000	8.88E-05	3.05E-04	1.16E-04	2.34E-04
0.1	1	7.5	1000	7.71E-05	2.28E-04	9.55E-05	1.84E-04
0.1	1	15	1000	7.20E-05	1.63E-04	8.46E-05	1.36E-04
0.1	1	30	1000	7.37E-05	1.12E-04	8.13E-05	9.63E-05
			Mass deposited	8.95E-04	2.27E-03	1.07E-03	1.51E-03
			Thoracic deposition	3.17E-03		2.58E-03	

Table 4. Monodisperse Particle Exposures: Fine and Coarse Deposited Mass

Particle Characteristics		Breathing Parameters		Deposition (mg)			
Diameter (μm)	σ_g	BF	Tidal Vol. (ml)	(Small Lung)		(Large Lung)	
				TB	P	TB	P
1	1	7.5	500	0.0160	0.0418	0.0199	0.0157
1	1	15	500	0.0159	0.0248	0.0175	0.0091
1	1	30	500	0.0175	0.0146	0.0175	0.0052
1	1	60	500	0.0211	0.0088	0.0195	0.0031
1	1	3.75	1000	0.0340	0.1187	0.0466	0.1099
1	1	7.5	1000	0.0617	0.2478	0.0397	0.0690
1	1	15	1000	0.0365	0.0418	0.0386	0.0412
1	1	30	1000	0.0432	0.0250	0.0422	0.0240
			Mass Deposited	0.2459	0.5233	0.2415	0.2772
3	1	7.5	500	0.1781	0.6281	0.2899	0.2209
3	1	15	500	0.1450	0.4567	0.1978	0.1694
3	1	30	500	0.1732	0.2939	0.1535	0.1050
3	1	60	500	0.3353	0.1403	0.1515	0.0571
3	1	3.75	1000	0.4103	1.6107	0.7097	0.9925
3	1	7.5	1000	0.3222	1.2941	0.4723	0.9447
3	1	15	1000	0.3535	0.8373	0.3562	0.7150
3	1	30	1000	0.6573	0.4187	0.3375	0.4390
			Mass Deposited	2.5749	5.6798	2.6684	3.6436

5	1	7.5	500	1.4802	2.8535	2.3066	0.1
5	1	15	500	1.1308	2.5110	1.4855	0.8924
5	1	30	500	1.6121	1.4489	1.0335	0.6725
5	1	60	500	2.9883	0.2901	1.0900	0.3440
5	1	3.75	1000	3.2629	6.7918	5.8008	2.8883
5	1	7.5	1000	2.4155	6.3578	3.7144	3.7600
5	1	15	1000	3.2454	4.1033	2.4909	3.5452
5	1	30	1000	6.2747	0.9837	2.4018	2.3131
			Mass Deposited	22.4099	25.3401	20.3235	15.218

Table 5. Polydisperse Aerosol Exposures: Deposition Fractions

A. Small Lung

Visit	Particle Characteristics		Breathing Parameters		Deposition (mg)	
	MMAD (μm)	σ_g	BF	Tidal Vol. (ml)	TB	P
1	0.1	1.5	15	500	0.091	0.216
1	1	1.5	15	500	0.064	0.121
1	3	1.5	15	500	0.136	0.337
1	0.1	1.5	15	1000	0.089	0.211
1	1	1.5	15	1000	0.073	0.108
1	3	1.5	15	1000	0.183	0.302
2	0.1	2.5	15	500	0.109	0.232
2	1	2.5	15	500	0.089	0.165
2	3	2.5	15	500	0.216	0.269
2	0.1	2.5	15	1000	0.103	0.237
2	1	2.5	15	1000	0.112	0.142
2	3	2.5	15	1000	0.314	0.212

B. Large Lung

Visit	Particle Characteristics		Breathing Parameters		Deposition (mg)	
	MMAD (μm)	σ_g	BF	Tidal Vol. (ml)	TB	P
1	0.1	1.5	15	500	0.103	0.077
1	1	1.5	15	500	0.073	0.043

1	3	1.5	15	500	0.175	0.121
1	0.1	1.5	15	1000	0.105	0.168
1	1	1.5	15	1000	0.079	0.096
1	3	1.5	15	1000	0.163	0.262
2	0.1	2.5	15	500	0.124	0.081
2	1	2.5	15	500	0.101	0.059
2	3	2.5	15	500	0.244	0.094
2	0.1	2.5	15	1000	0.124	0.179
2	1	2.5	15	1000	0.105	0.130
2	3	2.5	15	1000	0.238	0.207

Table 6. Polydisperse Aerosol Exposures: Deposited Mass

A. Small Lung

Visit	Particle Characteristics		Breathing Parameters		Deposition (mg)	
	MMAD (μm)	σ_g	BF	Tidal Vol. (ml)	TB	P
1	0.1	1.5	15	500	3.81E-05	9.05E-05
1	1	1.5	15	500	1.68E-02	3.16E-02
1	3	1.5	15	500	1.84E-01	4.56E-01
1	0.1	1.5	15	1000	7.46E-05	1.77E-04
1	1	1.5	15	1000	3.81E-02	5.63E-02
1	3	1.5	15	1000	4.86E-01	8.03E-01
				Mass deposited	0.7250	1.3473
				Thoracic deposition	2.0724	
2	0.1	2.5	15	500	4.57E-05	9.72E-05
2	1	2.5	15	500	2.33E-02	4.30E-02
2	3	2.5	15	500	2.80E-01	3.49E-01
2	0.1	2.5	15	1000	8.63E-05	1.99E-04
2	1	2.5	15	1000	5.82E-02	7.40E-02
2	3	2.5	15	1000	7.85E-01	5.29E-01
				Mass deposited	1.1465	0.9955
				Thoracic deposition	2.1419	

B. Large Lung

	Particle Characteristics	Breathing Parameters	Deposition (mg)
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Visit	MMAD (μm)	σ_g	BF	Tidal Vol. (ml)	TB	P
1	0.1	1.5	15	500	4.31E-05	3.23E-05
1	1	1.5	15	500	1.91E-02	1.13E-02
1	3	1.5	15	500	2.27E-01	1.57E-01
1	0.1	1.5	15	1000	8.80E-05	1.41E-04
1	1	1.5	15	1000	4.12E-02	5.01E-02
1	3	1.5	15	1000	4.07E-01	6.55E-01
				Mass deposited	0.6946	0.8739
				Thoracic deposition	1.5685	
2	0.1	2.5	15	500	5.19E-05	3.39E-05
2	1	2.5	15	500	2.62E-02	1.54E-02
2	3	2.5	15	500	3.17E-01	1.22E-01
2	0.1	2.5	15	1000	1.04E-04	1.50E-04
2	1	2.5	15	1000	5.46E-02	6.77E-02
2	3	2.5	15	1000	5.95E-01	5.17E-01
				Mass deposited	0.9934	0.7220
				Thoracic deposition	1.7154	

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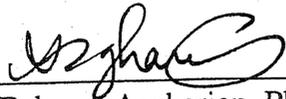
Assessment of Potential Maximum Dose in ADEPOSIT Subjects

Submitted to

Dr. James Samet
U. S. Environmental Protection Agency
58 D U.S. EPA Mailroom, Research Triangle Park, NC

Submitted by

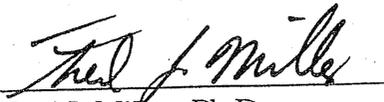
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Date



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3/15/02

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Objective

An independent study was conducted at CIIT Centers for Health Research to assess the dose received by 2 subjects (A21 & C05) in the protocol IRB#91-EPA 226 during a brief exposure to di (2-ethylhexyl) sebacate (DEHS) particles. These subjects corresponded to typical cases among asthmatic and chronic obstructive pulmonary disease (COPD) patient groups with the greatest potential risk for adverse effects as a result of exposure to the airborne materials.

Approach

The deposition calculations were carried out using the multiple-path lung deposition model of Anjilvel and Asgharian (1995). There are no lung morphometry measurements currently available on individuals with asthma or COPD. For the current analyses, the lung geometry of normal, healthy adults was used in the calculations since study subjects were only mildly diseased. Two adult human lung geometries with asymmetric branching structures in the tracheobronchial region (TB) were generated. The generated lung structures were based on the morphometric measurements of Raabe et al. (1976). Each lung consisted of a stochastically generated asymmetric branching structure in the TB region (Koblinger and Hofmann, 1990; Asgharian et al., 2001) completed by attaching an 8-generation symmetrical acinus (Yeh et al., 1979) to the end of the terminal bronchioles. These two lungs were selected from a pool of 30 stochastically generated lungs and represented limiting cases of the lungs with the smallest and largest number of TB airways. Incorporating the asymmetric feature of the lung structure allowed for more realistic assessment of the site-specific and local deposition of particles in the respiratory tract.

Subject Input Data

Various inputs such as the subject's lung parameters (e.g. functional residual capacity, head volume etc.) and breathing parameters (tidal volume, and breathing frequency) were necessary to perform the calculations. To obtain these data and to ensure that CIIT understood the manner in which Dr. Kim's study was conducted, a meeting was held with Drs. C. S. Kim, J. Samet, and B. Asgharian on Monday, March 4, 2002. The exposure

data and other necessary information were obtained to enable the CIIT team to calculate the dose received by these 2 individuals.

Dr. Kim stated that these 2 subjects were exposed orally for one day only to 5 μm -diameter monodisperse particles of mass density 0.89 g/cm^3 at a concentration of 50 mg/m^3 . The subjects did not return for any additional exposures. The highest dose to an individual was therefore at the end of the exposure day when there was no appreciable clearance. The results calculated in the report were thus limited to the deposition mass only. The breathing parameters and the exposure concentrations were identical for the 2 subjects. Each subject was trained to inhale 4 different volumes of air at various breathing flow rates. The breathing frequencies were calculated and are provided in Table 1 along with the tidal volumes for each exposure scenario. While we used the functional residual capacity (FRC) values supplied by Dr. Kim, the value for FRC of 6.91 liters for subject C05 is, in our opinion, highly suspect for an individual with mild COPD and should be verified by Dr. Kim.

Each subject was exposed to 11 different breathing scenarios on the exposure day. The number of breaths varied for each exposure scenario. The information on the number of breath per exposure scenario was provided by Dr. Kim for one individual (A21) and an estimate was given for the other subject (C05). Due to lack of information, it was assumed that the inhalation and exhalation times were equal and there was no pause between inhalation and exhalation. Default parameter values available in the literature were used when the values were missing.

Deposition fraction during one breathing cycle via mouth breathing was calculated for the two lung geometries using the FRC, breathing and lung parameters of the subjects, and particle size characteristics. Total and regional mass deposited in the respiratory tract in the subjects was subsequently calculated for each breathing scenario from the expression given below.

$$\text{Mass Deposited} = \text{Deposition Fraction} \times \text{Exposure Concentration} \times \text{Tidal Volume} \times \text{Number of Breaths}$$

The calculated deposition fraction in each region of the lung was substituted in the above equation to obtain the corresponding deposited mass.

Results

Tables 2–5 show the head, TB, pulmonary (PUL), and total deposition results in the 2 lung geometries for each breathing scenario. Accumulated mass deposited in each subject at the end of the day from inhaling the particles in various exposure scenarios is given in the last row of each table. Tables 2 and 3 give the calculated data for subject A21, while the data for subject C05 is given in Tables 4 and 5.

Despite oral breathing, a significant portion of the particles were removed from the inhaled air before reaching the lower respiratory tract. Nonetheless, deposition in the lower respiratory tract was significant. Patient A21, having a smaller FRC of almost half that of patient C05, showed a larger deposition fraction of the inhaled materials. The total deposition fraction varied between 80 to 98% for this patient. The mass amount of the total deposited material is similar for the 2 subjects (2.8 mg for A21 versus 2.5 mg for C05 where the values are the calculated average deposition in the 2 stochastic lungs). The amount deposited in the lower respiratory tract is larger for subject A21 (averages of 1.9 mg for A21 versus 1.3 mg for C05). This difference and the fact that patient A21 had a smaller FRC (and thus smaller lung) are probably why the deposited mass per unit surface area was significantly higher.

Finally, it should be mentioned that the dose to the subjects exceeded the value of 50 μm given in the protocol by 50 to 60 fold. The calculated total deposited mass in patient A21 is about 0.95 mg higher than that in the analyses provided by Dr. Kim (1.85 mg). Since this patient has a smaller than average lung size, it is likely that uncertainty regarding use of the default values contributed to the difference in deposition results. The calculated deposited mass in patient C05 matches that of Dr. Kim closely (2.5 mg versus 2.4 mg).

Table 1. Breathing parameters of the subjects during the exposures as provided by Dr. Kim.^a

Tidal Volume (cm ³)	Breathing Period (s)	Breathing Frequency (min ⁻¹)
350	4	15.00
350	2.8	21.43
500	6.66	9.01
500	4	15.00
500	2	30.00
750	6	10.00
750	4	15.00
750	3	20.00
1000	8	7.50
1000	4	15.00
1000	2	30.00

^a The functional residual capacity values supplied by Dr. Kim for subjects A21 and C05 were 3.05 and 6.91 liters, respectively.

Table 2. Deposited mass of particles in subject A21 with FRC =3.05 liters using a lung geometry with the smallest number of TB airways.

Number of Breaths	Deposition Fraction				Deposited Mass (mg)			
	Head	TB	PUL	Total	Head	TB	PUL	Total
8	0.275	0.163	0.366	0.804	0.039	0.023	0.051	0.113
11	0.346	0.169	0.311	0.826	0.067	0.033	0.060	0.159
8	0.189	0.181	0.481	0.851	0.038	0.036	0.096	0.170
11	0.271	0.178	0.42	0.869	0.075	0.049	0.116	0.239
10	0.354	0.333	0.23	0.917	0.089	0.083	0.058	0.229
8	0.209	0.184	0.511	0.904	0.063	0.055	0.153	0.271
11	0.263	0.24	0.416	0.919	0.108	0.099	0.172	0.379
10	0.287	0.335	0.312	0.935	0.108	0.126	0.117	0.351
6	0.176	0.186	0.559	0.922	0.053	0.056	0.168	0.277
7	0.249	0.329	0.366	0.945	0.087	0.115	0.128	0.331
7	0.208	0.7	0.075	0.983	0.073	0.245	0.026	0.344
Accumulated total mass (mg):					0.797	0.920	1.144	2.862

Table 3. Deposited mass of particles in subject A21 with FRC =3.05 liters using the lung geometry with the largest number of TB airways.

Number of Breaths	Deposition Fraction				Deposited Mass (mg)			
	Head	TB	PUL	Total	Head	TB	PUL	Total
8	0.373	0.233	0.114	0.72	0.052	0.033	0.016	0.101
11	0.457	0.198	0.105	0.759	0.088	0.038	0.020	0.146
8	0.26	0.302	0.217	0.78	0.052	0.060	0.043	0.156
11	0.36	0.233	0.223	0.816	0.099	0.064	0.061	0.224
10	0.492	0.214	0.17	0.875	0.123	0.054	0.043	0.219
8	0.273	0.26	0.331	0.865	0.082	0.078	0.099	0.260
11	0.342	0.227	0.319	0.888	0.141	0.094	0.132	0.366
10	0.388	0.228	0.289	0.905	0.146	0.086	0.108	0.339
6	0.228	0.276	0.386	0.891	0.068	0.083	0.116	0.267
7	0.329	0.235	0.357	0.921	0.115	0.082	0.125	0.322
7	0.359	0.41	0.192	0.961	0.126	0.144	0.067	0.336
Accumulated total mass (mg):					1.092	0.814	0.831	2.737

Table 4. Deposited mass of particles in subject C05 with FRC =6.91 liters using a lung geometry with the smallest number of TB airways.

Number of Breaths	Deposition Fraction				Deposited Mass (mg)			
	Head	TB	PUL	Total	Head	TB	PUL	Total
9	0.363	0.179	0.187	0.729	0.057	0.028	0.029	0.115
9	0.452	0.153	0.157	0.762	0.071	0.024	0.025	0.120
6	0.246	0.217	0.331	0.794	0.037	0.033	0.050	0.119
11	0.356	0.170	0.293	0.818	0.098	0.047	0.081	0.225
10	0.511	0.164	0.194	0.870	0.128	0.041	0.049	0.218
8	0.263	0.181	0.427	0.871	0.079	0.054	0.128	0.261
11	0.345	0.166	0.376	0.886	0.142	0.068	0.155	0.365
9	0.404	0.174	0.322	0.900	0.136	0.059	0.109	0.304
6	0.214	0.188	0.497	0.899	0.064	0.056	0.149	0.270
7	0.336	0.177	0.405	0.919	0.118	0.062	0.142	0.322
6	0.412	0.326	0.215	0.953	0.124	0.098	0.065	0.286
Accumulated total mass (mg):					1.054	0.570	0.980	2.604

Table 5. Deposited mass of particles in subject C05 with FRC =6.91 liters using a lung geometry with the largest number of TB airways.

Number of Breaths	Deposition Fraction				Deposited Mass (mg)			
	Head	TB	PUL	Total	Head	TB	PUL	Total
9	0.479	0.149	0.002	0.63	0.075	0.023	0.000	0.099
9	0.568	0.122	0.002	0.693	0.089	0.019	0.000	0.109
6	0.366	0.277	0.032	0.675	0.055	0.042	0.005	0.101
11	0.496	0.208	0.03	0.734	0.136	0.057	0.008	0.202
10	0.653	0.153	0.021	0.827	0.163	0.038	0.005	0.207
8	0.384	0.282	0.133	0.799	0.115	0.085	0.040	0.240
11	0.478	0.227	0.128	0.833	0.197	0.094	0.053	0.344
9	0.542	0.201	0.116	0.859	0.183	0.068	0.039	0.290
6	0.312	0.317	0.211	0.841	0.094	0.095	0.063	0.252
7	0.453	0.223	0.209	0.884	0.159	0.078	0.073	0.309
6	0.573	0.208	0.147	0.929	0.172	0.062	0.044	0.279
Accumulated total mass (mg):					1.439	0.661	0.331	2.432

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OFFICE OF
RESEARCH AND DEVELOPMENT

July 9, 2004

MEMORANDUM

SUBJECT: Annual Update on HSD Human Subjects Progressive Action Plan

FROM: Hal Zenick, Ph.D. *HZ*
Associate Director of Health, NHEERL (B105-01)

TO: Peter Preuss, Ph.D.
EPA Human Studies Research Review Official (8601D)

I am pleased to submit the Human Studies Division's Annual Update on HSD Human Subjects Progressive Action Plan (previously referred to as Corrective Action Plan). The Division continues to make significant progress in addressing, and exceeding, the recommendations provided by the external review panel in August 2002. NHEERL is committed to a continued, diligent pursuit of the highest ethical and safety standards and practices in the conduct of studies involving human subjects. We appreciate the support and advice provided by your office over the past year and look forward to a continued, close working relationship.

cc: Kevin Y. Teichman
John Jones
Rebecca L. Calderon
William F. McDonnell

Attachment (3)

Human Subjects Research Progressive Action Plan

Human Studies Division, NHEERL, U.S. EPA

July 1, 2004

I. Reporting Incidents and Responsiveness

Recommendation 1: ORD needs to develop a well-defined, streamlined process for when and to whom non-compliance should be reported.

Action: This plan is in place. The responsibility of investigators is to inform the IRB and HSD management should noncompliance or an adverse event be discovered. HSD management reports the incident to the next level of ORD management until the appropriate notification level is reached. At this stage all issues go to the NHEERL Human Subjects Official, the Division Director, and the Associate Director for Health, who then decides if it needs to be brought to the attention of the Agency.

Recommendation 2: A process is needed for timely, efficient action relative to the protection of human subjects (in the event of non-compliance).

Action: A study found to be in non-compliance would be interrupted until any problems were corrected and until resumption of the study was allowed by the IRB and HSD or higher EPA management.

Recommendation 3: A streamlined process is needed to facilitate notification of subjects.

Action: In the event that it is deemed necessary to contact previous volunteers in any study, addresses, telephone numbers, and other information contained in research and medical charts would be utilized. In addition the timely location of "lost" subjects is covered within the statement of work in the contract with the EPA recruitment contractor. The process of communicating with volunteers would be overseen by the Director of the NHEERL Human Research Protocol Office in conjunction with the Principal Investigator and the IRB of record.

II. Assuring Dose Delivered to Subjects

Recommendation 4: NHEERL must assure with absolute certainty the dose delivered to subjects, including independent verification of stability, homogeneity, and concentrations of dosing solutions prior to subject exposure.

Action: This policy is directed toward exposure to material not prepared and delivered by TRC Environmental Corp., the on-site operations and maintenance contractor.

The TRC exposure monitoring system and its oversight is state of the art and is being sustained. For the non-TRC exposures to environmental agents, an independent laboratory such as the UNC investigational drug pharmacy will provide, under contract, independent verification of concentrations of dosing solutions. An exception to this is the procedure for preparation of drug solutions (e.g. methacholine solutions for bronchial inhalation challenge testing) which are available prepackaged in USP grade and therefore of known purity, stability, and weight. These solutions will be prepared by two investigators/technicians following an acceptable standard operating procedure which has been approved by the HSD Quality Assurance Officer.

Recommendation 5: Each principal investigator must identify an acceptable range for delivered dose (or concentration of dosing solutions) for each protocol to more precisely determine when an incorrect dosing event has occurred.

Action: Protocols active in 2002 underwent a review, and all new protocols are reviewed to insure that ranges of acceptable exposure (dose) are provided rather than just the target dose. This is reviewed by the branch chief early in the development of the protocol and again later by the division director, division QA officer, and the Director of the NHEERL Human Research Protocol Office.

Recommendation 6: Measures of delivered dose should be included in all active protocols, whether or not the delivered dose is the parameter of concern.

Action: This has been included for all protocols approved since 2002.

Recommendation 7: Periodic re-review and audit of clinical studies to proactively identify and correct any problems, as well as improve study protocols should be undertaken.

Action: Ongoing clinical studies may be reviewed or audited by a team of QA experts and/or by the NHEERL Human Research Protocol Office.

Protocol Office File Review: We are currently reviewing files of all protocols contained in the NHEERL Protocol Office. Records of completed/closed studies are being archived. Files of all active studies are being reviewed for the presence of an EPA approval letter for the conduct of human research. Files of active studies conducted in an NHEERL facility and for which the UNC IRB is the IRB of record are also being reviewed for the presence of a current IRB approval. Files of active studies conducted off-site and for which the primary IRB is at another institution are also being reviewed for an original IRB approval. A tracking system will be implemented later in 2004 to allow ongoing tracking of current IRB approval for all active studies.

Protocol Office Technical Review: We will consider implementing a system for periodically auditing the performance of selected studies in 2005. This review might include such elements as observation of acquisition of informed consent,

comparison of the actual subject interactions with those specified in the protocol, and comparison of procedures for data privacy with those specified in the protocol, among others.

QA Technical Systems Review: The majority of clinical studies undergo a QA TSR review once during the course of the study. A team of QA experts reviews protocols, standard operating procedures, and written records related to dosing of volunteers and other procedures. In some cases, performance of procedures is observed. One purpose of the review is to ensure that the actual conduct of the study is consistent with the protocol and with the standard operating procedures.

III. Institutional Review Board Interactions Including the Subject Consent Process

Recommendation 8: Consider establishment of a centralized Protocol Office.

Action: This has been done for all human research conducted within NHEERL. The review process for human studies is coordinated within this office, all records are stored here, and studies are tracked for current IRB approval, among other things. The Director of the NHEERL Human Research Protocol Office will continue to provide leadership in promoting a culture of safe, ethical conduct of human research in the laboratory. The Director also maintains a close relationship with the UNC IRB and coordinates human research training and seminars within the laboratory.

Recommendation 9: Make EPA scientific review comments available to the IRB

Action: This is done for each protocol for which extramural review is required under the draft NHEERL Human Subjects Research Policy.

Recommendation 10: Use a consent auditor to identify ways in which the consent process can be improved.

Action: A seminar/workshop is being planned for fall 2004 focused on all aspects of the consent process. In 2005, we will have either intramural or extramural individuals audit the acquisition of informed consent with the goal of providing suggestions for improving the process.

Recommendation 11: Simplify consent form language.

Action: This topic will also be addressed in the training indicated above. Some aspects of the consent form cannot be changed without the permission of the UNC IRB. Since the training will likely be given by a member of the UNC IRB staff, this issue will be discussed at the time.

Recommendation 12: Add subject's initial blank at the bottom of each consent form page.

Action: This has been done.

Recommendation 13: Add more complete investigator and subject certification statements.

Action: This is being done consistent with the guidelines of our IRB.

Recommendation 14: Consent forms should list all investigators and their phone numbers and a 24-hour contact number.

All investigators are listed on the consent forms, and the phone number of the Principal Investigator, the Director of the NHEERL Human Research Protocol Office, and the Head of the UNC IRB are listed. We do not believe that there is a need to list the phone numbers of other investigators. A toll-free telephone number with an answering machine will be provided for participants to request a return call concerning a study in which they are participating. For studies in which medical issues might reasonably be expected to arise (e.g. fever several hours after the performance of a bronchoalveolar lavage), the PI will ensure that a physician will be on-call 24 hours per day for an appropriate period following the procedure.

Recommendation 15: A designated institutional official should be provided with copies of all pertinent IRB meeting minutes.

The Director of the NHEERL Human Research Protocol Office receives those minutes from the UNC IRB.

IV. Training, Mentoring, and Development of a Culture of Safety

Recommendation 16: Simulations or dry-run exercises with appropriate levels of physical or psychological fidelity should be undertaken as a technique for training and assessing new quality control processes or rapid-pressured decision-making responses to potential subject complications.

Action: Field studies conduct extensive training of field staff and usually run a limited number of subjects to assure that procedures can be implemented as designed. Simulations or dry-runs are required when appropriate for controlled exposure studies using new methods or exposure protocols. The HSD medical staff routinely conduct "code" drills to practice emergency techniques.

Recommendation 17: HSD should establish a safety culture to ensure that a concern for safety is actively maintained on an ongoing basis. Bring in safety experts as speakers or seminar leaders from related disciplines, institute a speaker series.

Action: This has been slowly implemented with presentations by Dr. Kerm Henricksen in December 2002 and with a presentation/workshop by Dr. Dan Nelson, head of the

UNC IRBs in February 2004. Dr. Nelson's presentation was videoconferenced to investigators and management in RTP. Dr. Nelson or a member of this staff will return in fall of 2004 for another workshop on improving the process of obtaining informed consent. Other workshops tailored to HSD concerns will occur twice a year. Establishment of a safety culture can only be accomplished if management at all levels is committed to this goal. See below for management training.

Recommendation 18: Conduct brainstorming sessions focused on areas of vulnerability.

Action: These sessions now occur informally among the Director of the NHEERL Human Research Protocol Office, the HSD medical station staff, the HSD recruitment contractor, and selected members of management and investigators. A more formal session focused on identifying areas of vulnerability will be conducted at the next HSD retreat in 2004.

Recommendation 19: Identify means of training of upper management to gain exposure to new concepts and principals of safety.

Action: A draft NHEERL Human Research Policy and Procedures document has been completed and circulated to NHEERL management. All training seminars/workshops conducted in HSD will be videoconferenced to RTP and other locations for attendance by management and investigators alike. The Director of the NHEERL Human Research Protocol Office is scheduled to make a presentation to a meeting of Laboratory management in the summer of 2004. The subject will be an introduction to human research ethics and requirements as well as a review of the Policy and Procedures document.

Recommendation 20: Institute specific training related to technical and equipment-related study aspects.

Action: This is done on an ongoing basis for on-site situations and is coordinated by appropriate personnel (e.g. medical station staff for the new EKG telemetry monitoring system or an individual PI for a new spirometry system). Field studies personnel were required to take annual training on April 13, 2004. In addition, investigators who have no previous experience with a technique that might be used in a study (e.g. induced sputum, exhaled breath) must be approved by the Medical Station prior to performing that technique on a subject.

Recommendation 21: Create check lists of required screening procedures and activities, including signed consent forms.

Action: This topic is under consideration.

Recommendation 22: Develop and implement a comprehensive mentoring program.

Action:

This is a division management activity with participation by appropriate NHEERL human research ethics personnel, and improvements in this area are under consideration. Currently branch chiefs hold regular meetings with post-docs, and the HSD division director meets at least once per year with the post-docs. The Director of the NHEERL Human Research Protocol Office gave a talk on human research to the NHEERL Training Organization in June 2004. Investigators without prior human study experience will not be allowed to be the PI of a study; they must first serve as a co-PI under the mentorship of an experienced PI.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
RESEARCH TRIANGLE PARK, NC 27711

April 4, 2002

MEMORANDUM

SUBJECT: Exposure of Subjects to Sebacate Particles in ADEPOSIT

FROM: Robert Devlin, Chief *R Devlin*
Clinical Research Branch

TO: John Vandenberg, Acting Director
Human Studies Division

Dr. Kim was asked to calculate the maximum dose of 5 micron particles delivered to each of the subjects in his study. His calculations are appended to this letter as "Estimation of maximum dose of ADEPOSIT subjects." The maximum dose varied from 0.89 – 2.69 mg. To validate the approach taken by Dr. Kim in arriving at these calculations, two outside dosimetry experts from CIIT were asked to perform an independent analysis on data provided for two subjects, who represent a "typical" subject and one with the greatest potential risk for adverse effects as a result of exposure to airborne materials (a subject with COPD). The calculations were carried out using the model of Anjilvel and Asgharian (1995) and attached to this letter as "Assessment of Potential Maximum Dose in ADEPOSIT Subjects." Their report concludes that the approach taken by Dr. Kim was valid.

Note that three different size particles were used in this study. These calculations were performed on exposures in which the largest size particles (5 microns) were used, since that would result in the largest mass of particles delivered to the lung. However, some subjects were exposed to 3 micron and 1 micron particles, in addition to 5 micron particles. These exposures were separated by a few days or up to a few weeks. Taking into account clearance of particles after each exposure, Dr. Kim has calculated that the additional particle dose delivered to these subjects may be estimated by multiplying the dose received with 5 micron particles by 1.3. A copy of his e mail explaining these calculations is appended to this letter.

Dr. Bennett, a researcher at UNC who is an expert in human dosimetry, was asked to compare the dose received by Dr. Kim's subjects to that received by humans in other dosimetry studies. After reading several papers in which humans were exposed to the same kind of particles as used in Dr. Kim's study, Dr. Bennett was unable to make a direct comparison – primarily because the papers did not contain sufficient details (such as the number of breaths of particles each subject

inhaled) to allow a calculation of total dose delivered. However, it was able to calculate the concentration of 1, 3, 5 micron particles used in those studies. One such paper is attached to this letter (Brand et al., 1999). In this paper subjects were exposed to a particle concentration of 260 mg/m³ and there were no reported adverse health effects associated with the study. Dr. Kim's subjects were exposed to a maximum particle concentration of 150 mg/m³ with no reported adverse health effects. Assuming subjects in both studies were using the same breathing pattern, Dr. Kim's subjects inhaled only 58% as much particle mass as the subjects in the Brand study.

Estimation of maximum dose of ADEPOSIT subjects

In ADEPOSIT study, deposition fraction of inhaled inert oil aerosols (1, 3 and 5 μm diameter) is measured *in situ* in volunteer subjects. Subjects visit the lab three times on different days and DF is measured for one size aerosol in each visit. On a study day, subjects inhale a test aerosol up to 12 breaths with a predetermined breathing pattern, and the same procedure is repeated with six to twelve different breathing patterns. Therefore, the subject may inhale the aerosol up to 144 breaths. The actual lung deposition dose may be assessed by the following relationship:

$$D_i = C_i \cdot V_i \cdot DF_i \quad \text{for each breath}$$

$$D = C \cdot V \cdot DF \cdot N \quad \text{for total}$$

where D_i = deposition dose for *i-th* breath

C_i = concentration of inhaled aerosol for a given breath ($\mu\text{g}/\text{liter}$)

V_i = tidal volume, volume of *i-th* breath (liter)

DF_i = deposition fraction of *i-th* breath ($DF = 1 - \text{exhaled/inhaled}$)

D = total deposition dose for all breath (μg)

N = total number of breaths inhaled

C, V, DF = average of all breaths

Here, D_i varies breath by breath because the subject cannot maintain the exact same breath during inhalation. D_i and N also vary for different subjects. Tracking down the breath by breath variation of these values is practically impossible. However, the values can be averaged over a number of breaths and the total number of breaths inhaled may be estimated from the average data. During the study, C_i is not measured, but monitored by an electric signal. The default value is about 6 volt that corresponds to about 50 $\mu\text{g}/\text{l}$ concentration for 5 μm aerosol. Dose estimation is attempted for 5 μm aerosol only because the dose of smaller size particles is much smaller. The summary of individual dose estimation is given in the Table.

Maximum dose estimation for ADEPOSIT subjects

Normal subjects		Elderly subjects		Asthmatic subjects		COPD subjects	
Subj #	Dose (mg)	Subj #	Dose (mg)	Subj #	Dose (mg)	Subj #	Dose (mg)
N01	1.78	E03	1.90	A01	1.20	C01	2.64
N02*	1.00	E04	1.69	A02	1.10	C02	2.25
N03	1.91	E05	1.86	A03	1.17	C03	2.55
N05	2.15	E06	1.63	A04	1.06	C04	2.69
N06	1.91	E07	1.52	A05	1.04	C05	2.39
N08	1.87	E08	1.76	A06	0.89	C06	2.17
N09	2.28	E09	1.51	A07	0.97		
N11	2.23	E10	1.47	A08	1.94		
N12	2.27	E11	2.10	A09	2.40		
N13	2.04	E12	1.61	A10	2.15		
N14	2.00	E13	2.06	A11	2.17		
N15	2.08	E14	1.93	A12	2.19		
N17	2.13	E15	2.02	A13*	0.70		
		E16	1.65	A14*	0.10		
		E17	1.93	A15	2.29		
		E18	1.76	A16	2.22		
		E19	2.13	A17*	0.72		
				A19	2.24		
				A20	2.16		
				A21	1.85		
Highest	2.28	2.13		2.40		2.69	
Lowest	1.00	1.51		0.10		2.17	
Mean	1.97	1.79		1.53		2.45	

* Partial study

Total Deposition of Therapeutic Particles During Spontaneous and Controlled Inhalations

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ABSTRACT: Treatment of systemic diseases by means of the inhalation route is hampered by uncertainties of the drug dose applied by inhalation. In this study, the hypothesis was tested that by standardization of the breathing maneuver used for inhalation, the interindividual variability of the dose deposited intrathoracically can be reduced. Therefore, breathing pattern during routine inhalations with jet nebulizers was measured in 18 patients with lung disease. Using monodisperse 3 μm particles, total deposition was then assessed for the measured spontaneous and for three controlled, slow breathing patterns. Particle deposition for the three controlled breathing patterns was additionally measured in 14 healthy subjects. The study has shown that within the study population the inhaled air volume and flow rate were quite different. Consequently, total particle deposition varied between 20 and 95%, depending on breathing pattern. For controlled, slow breathing patterns, deposition was on average higher, intersubject variability of deposition was smaller, and differences in deposition between healthy subjects and patients were negligible. Therefore, to perform efficient systemic treatment with aerosolized drugs, controlled, slow breathing patterns should be used. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association *J Pharm Sci* 89: 724–731, 2000

Keywords: particle deposition; variability; breathing pattern

INTRODUCTION

For many decades it has been well known that drugs for systemic therapy may be administered by means of the lungs. Since 1925, it has been known that inhaled insulin decreases the blood glucose level.¹ Nowadays, despite considerable progress in nebulizer technique and increased knowledge about particle deposition in the lung and drug absorption from lung surfaces, insulin administration by means of the lung is still not established but has reached a state of advanced clinical studies. The main reason for this slow-

ness of progress is related to uncertainties in the dose of drug administered by the inhalation route. The dose depends on many factors that are difficult to control: particle deposition in the lungs strongly depends on particle size, lung structure, and breathing pattern, with the result that particle deposition and thus the deposited dose varies considerably among patients.

In this study the hypothesis was tested that standardizing the breathing pattern decreases the intersubject variability of the dose deposited intrathoracically during inhalations of therapeutic particles generated with jet nebulizers. Therefore, in 18 patients deposition of inhaled monodisperse inert test particles was measured for the breathing pattern they used during routine inhalations with jet nebulizers and for three standardized patterns. In addition, particle deposition was

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measured in 14 healthy subject for these standardized patterns.

METHODS

Subjects

Eighteen patients, 12 men and 6 women, who were used to aerosol therapy with jet nebulizers and 14 healthy subjects, 8 men and 6 women, participated in this study (Table 1). Eight patients had chronic obstructive pulmonary disease, seven patients had bronchial asthma, one patient had bronchiectasis, one patient had silicosis, and one patient had primary ciliary dyskinesia. Conventional pulmonary function tests were performed by use of a Jäger-Masterlab (Erich Jaeger GmbH, Würzburg, Germany). Relative values of the lung function parameters (%pred) were calculated as proposed by the European Community for Coal and Steel.² Informed written consent was obtained from each subject. The study protocol was approved by the Ethics Committee of the Medical School of the Ludwig-Maximilians-University (Munich, Germany).

Spontaneous Breathing Patterns

The breathing pattern of patients during routine inhalations with jet nebulizers (Pari-LC+ nebulizers, Pari GmbH, Starnberg, Germany, pressure 0.17 M Pa) was measured as follows: An ultrasonic transient-time flowmeter (TUBA, GHG AG, Zürich, Switzerland) was connected to the Venturi channel (air inlet) of the nebulizer. The analogous flow signal was recorded by a personal computer (Intel 386 CPU) with a analog-digital converter (Data Translation DT2821), and the flow rate through the nebulizer nozzle was added. This air flow through the nebulizer nozzle was

measured for each nebulizer before inhalation. All patients were instructed to perform inhalations as usual until 2.5 mL of a salbutamol inhalation solution (GlaxoWellcome, 1.5 mg salbutamol sulphate in isotonic NaCl solution) was completely nebulized. From the recorded flow rates of each breath the average spontaneous tidal volume, V_t , and flow rate, Q_i , were calculated for each patient.

Deposition

To measure total deposition of aerosol for various breathing patterns, a monodisperse inert test aerosol consisting of di-2-ethylhexyl sebacate (DEHS) droplets was used. Deposition measurements were performed using a device in which a laser aerosol photometer³ is combined with an piston-type ventilator, allowing the subject to inhale particles at controlled breathing patterns (Fig. 1). The ventilator has a volume of 2 L and is driven by a computer-controlled step motor. A system of computer-controlled magnetic valves allows us to connect the ventilator to ambient air, to an aerosol supply, or to a mouthpiece at which the subject wearing a noseclip is located. After the ventilator was filled with aerosol, the subject tried to inhale at the mouthpiece, causing an underpressure that initiated the step motor. Thus, aerosol is inhaled at a preselected flow rate, Q_i . After inhalation of the desired aerosol volume, the direction of the ventilator was inverted and the subject exhaled into the ventilator at the preselected flow rate.

During the entire breathing cycle the laser aerosol photometer recorded the respired particle number concentration. Aerosol particle deposition, D , was calculated by integrating the particle number concentration, C , over the inhaled, V_i ,

Table 1. Lung Function Parameters of the Study Population

Parameter	Patients		Normals	
Number	18		14	
Sex	12 m/6 f		8 m/6 f	
Age (yrs)	60 ± 16		35 ± 6	
VC	3.1 ± 0.91	90 ± 19% pred	5.3 ± 1.1	113 ± 10% pred
TLC	6.4 ± 1.11	103 ± 14% pred	6.9 ± 1.1	107 ± 7% pred
ITGV	4.4 ± 1.51	143 ± 42% pred	3.6 ± 0.71	112 ± 19% pred
FEV ₁	1.78 ± 1.11	66 ± 34% pred	4.0 ± 0.91	106 ± 13% pred

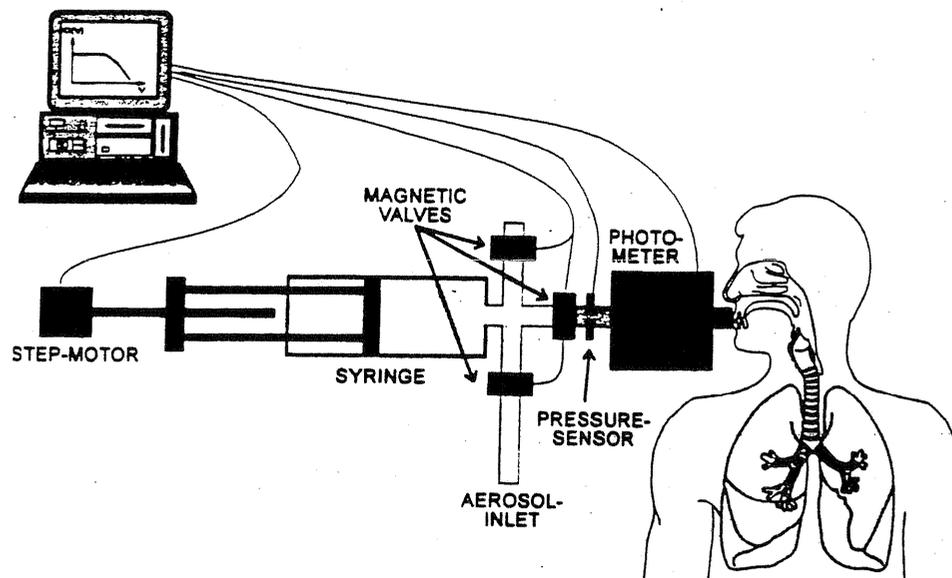


Figure 1. Schematics of the device for the measurement of lung deposition.

and exhaled volume, V_e :

$$D = 1 - \frac{\int_{V_e} CdV}{\int_{V_i} CdV}$$

In this study the following breathing patterns were performed by each subject:

Spontaneous breathing:

$$V_i = V_e = V_t, \quad Q_i = Q_e = Q_t$$

Very slow controlled breathing:

$$V_i = V_e = 1L, \quad Q_i = Q_e = 100 \text{ cm}^3/\text{s}$$

Slow controlled breathing:

$$V_i = V_e = 1L, \quad Q_i = Q_e = 250 \text{ cm}^3/\text{s}$$

Normal controlled breathing:

$$V_i = V_e = 1L, \quad Q_i = Q_e = 500 \text{ cm}^3/\text{s}$$

For each breathing pattern particle deposition was measured twice in each subject. Healthy subjects performed only the three standardized breathing patterns.

Particle Generation and Classification

Monodisperse di-2-ethylhexyl sebacate (DEHS) droplets were produced by heterogeneous nucleation of DEHS vapor on NaCl nuclei in a nitrogen atmosphere using a Topas SLG 270 generator

(Palas, Karlsruhe, FRG). The aerosol was then diluted with particle-free air to achieve a particle number concentration of $2 \cdot 10^4 \text{ cm}^{-3}$. Particle size was measured in a convection-free sedimentation cell and throughout the study was $2.98 \mu\text{m} \pm 0.1 \mu\text{m}$, a typical particle diameter for medical nebulizers.⁴

Data Evaluation

All statistical calculations were performed using Statgraphics Plus for Windows 2.0 on a personal computer (Pentium II CPU). The significance of differences between group averages was tested using the Student's *t* test. Correlation analysis was performed using Pearson product-moment correlation analysis. The requested level for significance was $P = 0.05$.

RESULTS

Although all patients were carefully trained at the beginning of their inhalation therapy to perform inhalations deeply and slowly, the breathing pattern was quite different among patients (Fig. 2). Some patients inhaled with a tidal volume of about 250 cm^3 and flow rates less than $200 \text{ cm}^3/\text{s}$; others inhaled about $2,000 \text{ cm}^3$ with flow rate close to $1,000 \text{ cm}^3/\text{s}$. The intraindividual variability of the tidal volume was $25 \pm 10\%$ and that of flow rate $22 \pm 10\%$. There was a strong correlation

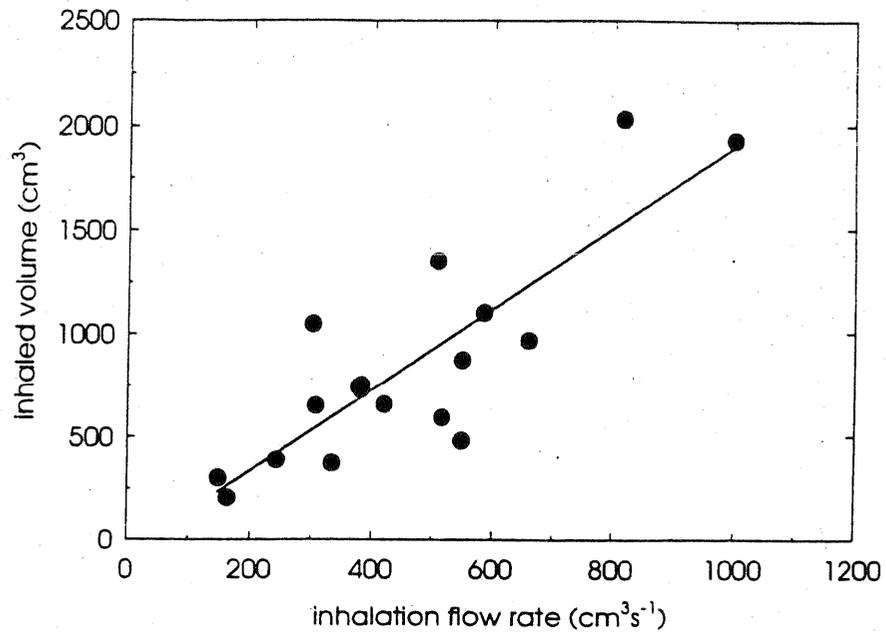


Figure 2. Tidal volume and flow rate measured in 18 patients with lung disease during spontaneous inhalations with a jet nebulizer.

between tidal volume and inhalation flow rate ($r = 0.84, P < 0.0001$): Thus, patients inhaling a large volume inhaled with a high flow rate; patients inhaling small volumes inhaled slowly with the result that the time of inhalation was nearly the same in all patients (1.8 ± 0.62 s).

Deposition of 3- μ m particles for spontaneous breathing pattern correlated strongly with the flow rate ($r = 0.76, P = 0.0002$) (Fig. 3) and the tidal volume ($r = 0.75, P = 0.0003$): patients inhaling a large volume at a high flow rate showed high aerosol deposition and vice versa. Average

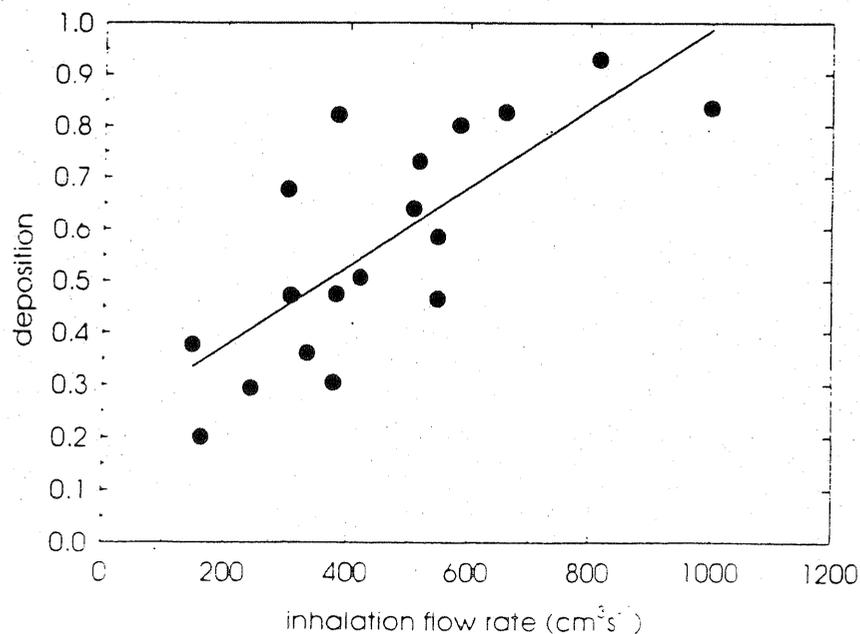


Figure 3. Particle deposition measured with test particles in 18 patients with lung disease as a function of inhalation flow rate.

total deposition in all patients was ($57 \pm 22\%$), exhibiting large intersubject variability: one patient showed deposition as low as 20%, whereas another patient reached deposition values of 95%. This variability was considerably reduced for controlled breathing (Fig. 4). Deposition was highest and the variability was lowest for very slow controlled breathing ($79 \pm 7\%$). For the slow breathing pattern deposition was significantly lower than for the very slow pattern ($70 \pm 10\%$, *t* test: $P = 0.01$). The normal breathing pattern showed similar deposition values as the slow pattern ($71 \pm 13\%$, *t* test, not significant). There was a significant correlation between deposition and flow rate ($r = -0.20$, $P = 0.04$). For all controlled breathing patterns there were no significant differences in aerosol deposition between patients and healthy subjects (Fig. 5). However, deposition in patients tended to be greater for the largest flow rate, and the variability of deposition was larger in patients for all flow rates. In healthy subjects deposition decreased significantly with increasing flow rate ($r = 0.74$, $P < 0.0001$). Again, deposition for the very slow breathing pattern was highest ($79 \pm 7\%$), lower for the slow breathing pattern ($71 \pm 4\%$, $P < 0.0001$), and again lower for the normal breathing pattern ($65 \pm 7\%$, $P = 0.007$). At a flow rate of $500 \text{ cm}^3/\text{s}$, deposition in patients correlated negatively with the extent of airway obstruction as measured by FEV_1 ($r = 0.72$, $P =$

0.002) (Fig. 6). Except for this obstruction dependency of deposition, no dependency on the kind of lung disease was observed in patients. At lower flow rates and in healthy subjects no significant correlations were observed (Fig. 7).

DISCUSSION

In this study total particle deposition was measured, but it was not possible to distinguish between extrathoracic, bronchial, and alveolar deposition. However, the total deposition values measured in this study are similar to the values given by a common deposition model.⁵ For the very slow breathing pattern and for $3\text{-}\mu\text{m}$ particles this model delivers a total deposition of 80%, which is in excellent agreement with the data measured in this study, and an extrathoracic deposition of 1.6%. For the faster patterns total deposition is 69 and 58%, and the extrathoracic deposition increases to 4 and 7.5%. Bronchial deposition given by this model is 9% for the very slow pattern and 3.5 and 3.6% for the faster inhalations. Because extrathoracic deposition supposed to be similar to that observed in healthy subjects in patients with lung disease, we conclude that total deposition measured in this study is a reasonable measure for intrathoracic deposition in humans.

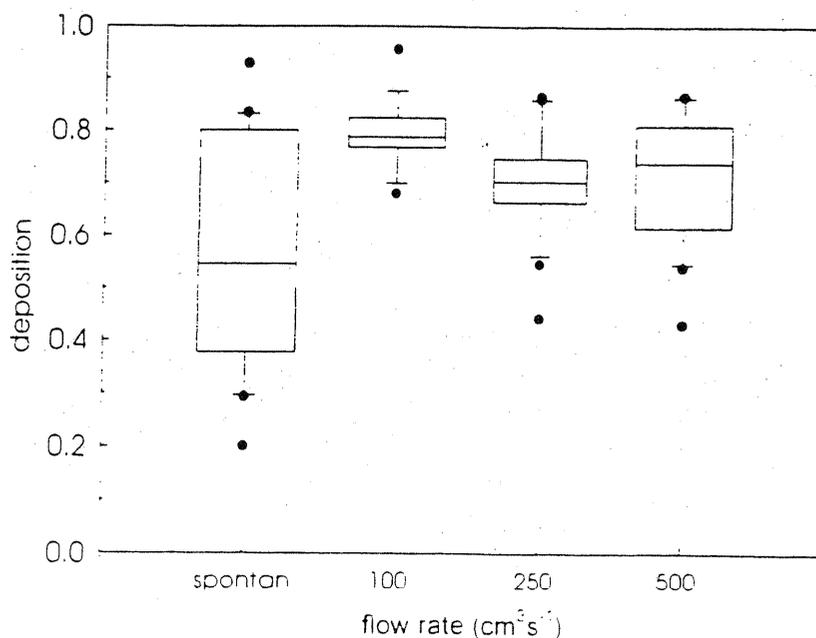


Figure 4. Particle deposition in 18 patients with lung disease at various breathing patterns.

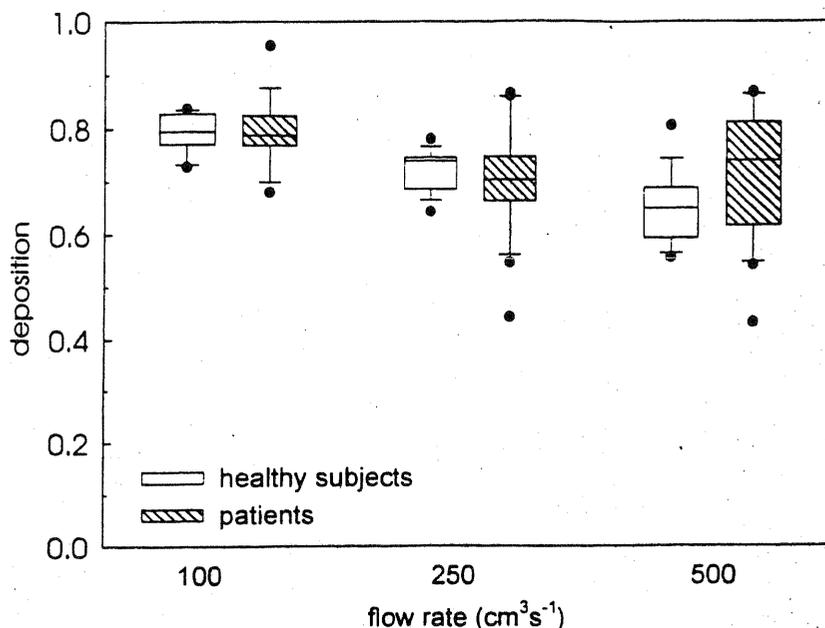


Figure 5. Particle deposition measured in 18 patients with lung disease and in 14 healthy subjects at three different breathing patterns.

For inhalation drug delivery requiring a precise dosage, the large intersubject variability of total deposition measured in this study for a spontaneous inhalation pattern is unacceptable. The data of this study show that the variability of particle deposition within the respiratory system can be considerably reduced if the breathing pattern

is controlled. The variability of deposition for the very slow breathing pattern was about three times smaller than the variability for the spontaneous pattern. This reduction in intersubject variability was air-flow rate dependent (Fig. 5). For slow and very slow flow rates deposition in healthy subjects and in patients is nearly identi-

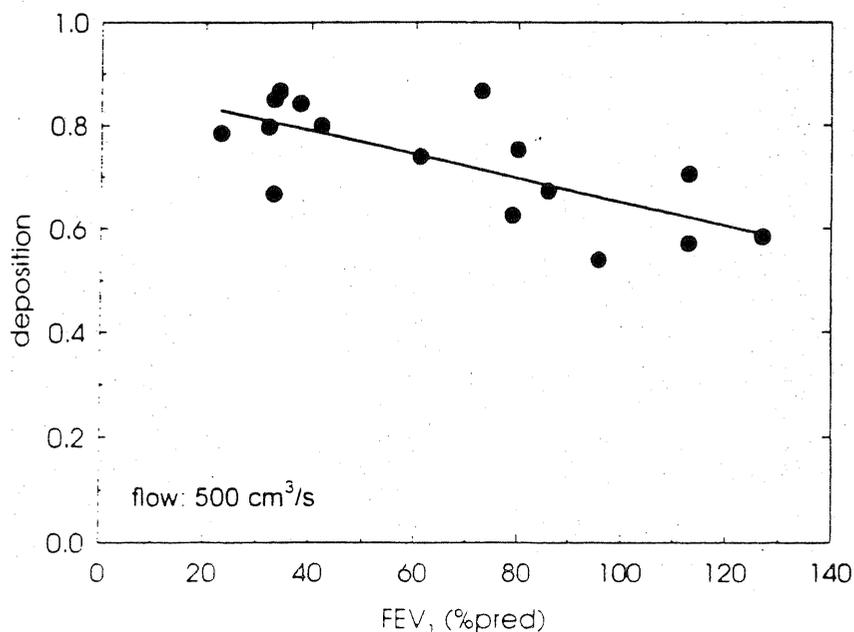


Figure 6. Particle deposition in 18 patients with lung disease at an inhalation flow rate of 500 cm³/s as a function of the forced expiratory volume in 1 s (FEV₁).

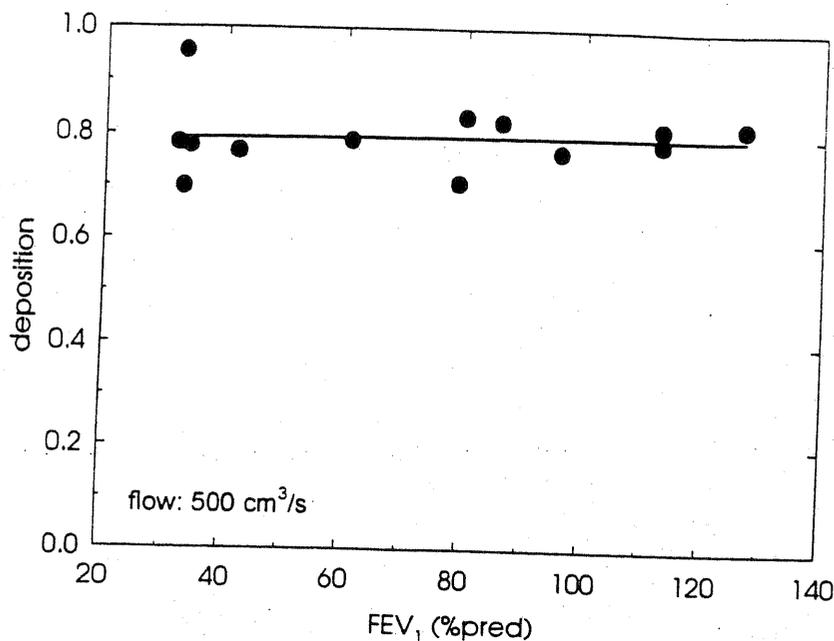


Figure 7. Particle deposition in 18 patients with lung disease at an inhalation flow rate of $100 \text{ cm}^3/\text{s}$ as a function of the forced expiratory volume in 1 s (FEV_1).

cal. Only for the highest air flow rate of $500 \text{ cm}^3/\text{s}$, patients tended to have higher deposition values than healthy subjects. If we assume that extra-thoracic deposition is small, this difference may be explained by particle impaction in obstructed airways at higher flow rates⁶⁻¹⁰. The strong correlation between FEV_1 and particle deposition (Fig. 6) illustrates that patients with normal FEV_1 (i.e., without airway obstruction) have the same deposition values as healthy subjects, whereas patients with decreased FEV_1 (i.e., with airway obstruction) show increased total deposition. This increase of total deposition in patients with airway obstruction is presumably due to increased inertial deposition within conducting airways. Because total deposition in patients and healthy subjects is the same for the very slow breathing pattern, it may be concluded that by inhaling very slowly, inertial deposition at obstructed airways can be prevented.

The implications of these results for an improvement of inhalation therapy are obvious. If a drug shall be applied to the lung periphery with high efficacy and low variability, inhalation should be performed slowly and controlled. In this case deposition is high (about 80%), the intersubject variability is low (9% for patients and 5% for subjects without lung disease), and deposition in obstructed airways may become negligible.

CONCLUSION

This study has shown that the intersubject variability of total particle deposition can be considerably reduced if the breathing pattern is controlled. If the inhalation flow rate is low, the variability is low and deposition at bronchial obstructions is supposed to be negligible. Therefore, the controlled breathing pattern with low flow rate is most suitable for targeting the lung periphery and thus for systemic aerosol therapy. If hormones like growth hormones or estradiol, heparin for surgery patients,^{11,12} α_1 -antitrypsin for patients with α_1 -antitrypsin deficiency,¹³ or prostacyclin for patients with pulmonary hypertension¹⁴ are administered by the inhalation route, this standardization of breathing patterns appears to be necessary.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

October 3, 2001

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Notice of Proposed Suspension

FROM: Linda S. Birnbaum, PhD., DABT *Linda S. Birnbaum*
Acting Director, Human Studies Division, MD-58A

TO: Chong Kim, PhD.
Human Studies Division, MD-58D

This memorandum is to advise you that I propose to suspend you from duty and pay status for twenty-one (21) calendar days from your position as Research Physical Scientist, GS-1301-15, Clinical Research Branch, Human Studies Division, National Health and Environmental Effects Research Laboratory (NHEERL), U.S. Environmental Protection Agency, Research Triangle Park, North Carolina. Should a decision be made to sustain this proposed action, the suspension will not begin any earlier than 30 calendar days following your receipt of this notice. This notice of proposed suspension is issued in accordance with Title 5, Code of Federal Regulations, Part 752. The specific reasons for this proposed action are as follows:

Charge: Disregard of a Directive (Federal Regulation)-EPA Order 1000.17 Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research (first offense)

Background: You have been employed with the U.S. Environmental Protection Agency since August 2, 1990, when you were hired at the top step of the GS-14, as a Research Physical Scientist, with the Human Studies Division, NHEERL. During the past eleven years, you have worked in the Division as a Research Scientist and have progressed to the GS-15 level after having become a National and World expert in the field of aerosol exposures.

As a senior research member and principal investigator (PI) in the Human Studies Division, conducting "hands on" research on human subjects, you are obligated to follow applicable guidelines and protocols that are in place to protect these human subjects and minimize the possibility of liability to the Government. The principal guideline that you

Attachment (6)

are to follow in carrying out these duties is 40 CFR, Part 26, (the Common Rule) titled Protection of Human Subjects, which is attached as Appendix A to EPA Order 1000.17A1, Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research, hereinafter called the Order, dated July 30, 1999. This Order discusses the functions of the Review Official and the Institutional Review Board (IRB). The Review Official is tasked with approving all EPA human studies research before the research starts to include approval of the research protocols to be employed in the study. The IRB monitors the studies once they have started and also approves/disapproves any proposed changes to the protocol methodology. The Order and its provisions are not guidance but are, in fact, the rule of law for conducting human research in the EPA. It is a fact that any changes to the research protocols have to be submitted to the IRB for approval before the change may take place. The responsibility for adhering to these rules falls to the principal investigator who has overall responsibility for the conduct of the research. One important requirement for human studies research is for the PI to prepare and update as necessary the informed consent form which is given to the study participant listing all the potential dangers and side effects resulting from his/her participation in the study. Any pollutant exposures must be listed on the form and there must be a discussion between the PI and the subject regarding the exposure amounts and the likelihood of adverse effects.

You have been involved for some time in a human studies project whereby volunteer subjects are exposed to particulate inhaled in a controlled setting. The particulate used in your most recent study is *diethyl sebacate*. On August 16, 2001, Dr. Philip Bromberg, M.D., University of North Carolina (UNC), Chapel Hill, notified your immediate supervisor, Jim Samet, PhD., in an e-mail of the following concern :

"After my relative euphoria of yesterday concerning possible improvements in the joint PM/dosimetry/modeling research program, I have learned this morning that the amounts of diethyl sebacate particles administered to volunteers in Chong's studies far exceeds what is stated in his approved protocol and consent form."

Incident to this report, an investigation was conducted regarding the conduct of your research and in particular your adherence to the research protocol established for the diethyl sebacate inhalations. As specified herein, it was determined that you had violated the research protocol in several areas.

Specification 1: Your protocol of record that was filed for this research stated the maximum particle size used in the inhalations would be not more than 50 mcg. The same dose was also stated on the consent form that each volunteer must read and sign. However, it was determined that you were knowingly conducting the experiment using deposited doses which may have exceeded approved levels. In some instances, the doses may have been greater than, or equal to, 1500 mcg, approximately 30 times larger than that listed in the protocol. It is not known at this time whether this increased particle mass has in fact had a detrimental effect on any of the human subjects used in the study. In any event, you used a particle size that was not disclosed to the subject via the

informed consent form nor was it listed in the research protocol. This unauthorized use of this size particle dose was in direct violation of the protocol and of the EPA Order 1000.17A1 and forms one basis for the charge "*Disregard of a Directive (Federal Regulation) -EPA Order 1000.17 Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research*" (first offense)."

Specification 2: It is a requirement that all research subjects be provided a copy of the informed consent form that they sign and that the PI or designated collaborator also sign the form indicating that the subject was briefed as to the hazards of the research. Such signed completed forms are to be on file before the volunteer subject begins participation in the study as stated in Section 26.117 of the Order. Additionally, each participant is to be provided a copy of his/her completed consent. In the review that was conducted of your research, it was determined that of 118 subjects, there were 18 subject charts in which neither you nor any of your collaborators signed the form. In seventeen (17) of these cases, the form was signed only by the subject. In one case, there were no signatures at all. Such lack of documented consent is in clear violation of the Order and forms another basis for the charge "*Disregard of a Directive (Federal Regulation) -EPA Order 1000.17 Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research*" (first offense)."

Specification 3: Your protocol of record that was filed for this research stated who would be the researcher and specifically who would handle the human subject. It is a requirement of the protocol to have all research collaborators approved by the IRB in any human studies research. This is to insure that anyone who would have an opportunity to be involved with hands on research with human subjects has the necessary credentials. It has been determined that you allowed involvement of a collaborator even though the collaborator had not been approved by the IRB. The collaborator's name was Jim Brown and although approval for his participation would have most likely been granted, you nonetheless allowed his participation without seeking or obtaining approval as mandated by the Order. This oversight on your part forms another basis for the charge "*Disregard of a Directive (Federal Regulation)-EPA Order 1000.17 Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research*" (first offense)."

These above cited deviations from the EPA policy and from established protocols and directives are of major concern and have threatened the continuation of the controlled human exposure studies by NHEERL and its collaborators at UNC and other organizations. While at this time it appears that no human subject have suffered any adverse effects from your cavalier disregard of the rules and regulations, we will not know for sure until a definitive study is done of the particular exposures for each subject. I need not emphasize how important strict compliance with the spirit and letter of the rules that govern research involving human research is to all of us. Even an innocent breach of compliance without any harm coming to the subject could have disastrous consequences. You are well aware of what happened at John Hopkins University when Ellen Roche, a 24-year old healthy participant in a study on asthma, died suddenly on

June 2 after inhaling *hexamethonium*, which restricts airways, as part of the study. Besides the attendant adverse publicity that ensued after the untimely death of Ms. Roche, the Government immediately halted all human research at the university following the incident and there is a continuing investigation into the matter.

In determining the proposed penalty for this offense, the Agency's Table of Offenses and Penalties, Appendix A, outlined in EPA Order 3120.1, Conduct and Discipline, was considered. The table lists a penalty range of a written reprimand to a fourteen (14) day suspension for a first offense of "disregard of directive" of which three specifications are listed. This twenty-one (21) day proposed suspension, while exceeding the recommended penalty for a first offense, is prompted by my consideration of applicable aggravating/mitigating factors. You are a long-term senior member of the HSD staff and thus are fully cognizant of the requirements for strict adherence to research protocols. You previously were admonished by memorandum dated December 18, 1997, by your previous supervisor Dr. Robert Devlin, Chief, Clinical Research Branch, regarding your violation of research protocols and were told not to allow any protocol violations to occur again. In that you were previously warned of the consequences of violating research protocols, I am increasing the recommended penalty. This twenty-one (21) day proposed suspension is being proposed to impress upon you the seriousness of your actions and will serve as a warning to you that further instances of these types of failings will neither be tolerated nor condoned.

This proposed suspension, if effected, will promote the efficiency of the Federal Service. You have the right to respond to this proposal orally and/or in writing including any request for consideration of an alternative discipline agreement (Article 39 of Collective Bargaining Agreement) by submitting your response to Dr. Harold Zenick, Associate Director for Health, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Alexander Drive, Research Triangle Park, North Carolina, 27711. Dr. Zenick may be reached at (919) 541-2283.

You will be allowed seven (7) calendar days from your receipt of this notice to submit your written response. Should you desire a meeting in which to present an oral reply to the charges, you must request a personal conference with Dr. Zenick, either in your written reply, or separately, if no written reply is made. Any request for an oral reply must be made within the seven (7) calendar day reply period. Any reply you make will be fully considered in making the final decision.

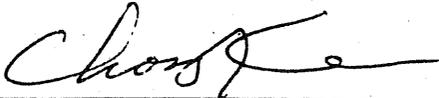
You have the right to review the material relied on in proposing this action. A copy of the material will be provided to you upon request to the Director, Human Resources Management Division. Subject to making satisfactory scheduling arrangements with your supervisor, you will be allowed up to eight (8) hours of official time to review the material relied upon to support this proposal, and/or to prepare a reply to this notice.

A decision will not be made on this proposed action until the expiration of the time allowed for reply. The decision will be based on the evidence of record, to include careful consideration of any written and/or oral response you may make. You will be notified in writing at the earliest practical date of the decision of this matter. You have the right to be represented by a representative of your choice, including self-representation. Any representation you choose must be designated in writing to Dr. Zenick.

You are asked to sign and date the acknowledgment copy of this letter provided. Your signature does not indicate agreement with the contents of this letter but merely indicates that you received it and any attachments thereof.

cc: Dr. Zenick (MD-87)
✓ Dr. James Samet (MD-58D)
Mary S. Day (MD-29)

RECEIPT ACKNOWLEDGED:



Name

10/3/01
Date



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

November 6, 2001

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Notice of Decision to Suspend

FROM: Harold Zenick, Ph.D. *HZ*
Associate Director for Health, NHEERL (MD-87)

TO: Chong S. Kim, Ph.D.
Research Physical Scientist (MD-58B)

By memorandum dated and received by you on October 3, 2001, Dr. Linda Birnbaum, Acting Director, Human Studies Division, National Health and Environmental Effects Research Laboratory (NHEERL), U.S. Environmental Protection Agency (EPA), Research Triangle Park, North Carolina, proposed that you be suspended for twenty-one (21) calendar days. The proposal was based on the charge of your "disregard of a directive (Federal regulation) - EPA Order 1000.17, Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research".

In that notice, you were informed of your right to reply both orally and in writing to the proposal and the seven (7) calendar day period to do so. On October 4, you sent me an email requesting an extension of the response time. On October 9, I granted your request to extend the response date to October 12, 2001. Accompanied by your representative, Robert L. Davis, you submitted a written statement and made an oral reply to me. I have thoroughly and carefully reviewed the evidence supporting this proposed action as well as your oral and written replies.

First, it is important to provide clarification of two separate activities: one focused on a redirection of your research and the second, addressing disciplinary actions, which is the substance of this memorandum. The former presented in a memorandum from Dr. Birnbaum to you on September 24, 2001, indefinitely banned you from the conduct of human studies with the directive to design a new research program. This assignment which is within the purview of management was done as a safeguard for human subjects protection because of a concern about your "inattention and complacency" in conducting human studies. It is within your prerogative to meet with Dr. Birnbaum to further discuss those actions. On the other hand, the memo from Dr. Birnbaum on October 3, 2001, focused on disciplinary action for these protocol violations and is distinct from the issue of work reassignment. It is within this context that this current letter is now issued.

Attachment (7)

Kim

November 6, 2001

Page 2

In your October 12th written and oral response, you stated that the proposed suspension action was based on "unintentional", "procedural", and/or clerical errors and further stated that "the incident (reported on August 15, 2001) has resulted in no adverse effects to the subjects and would have virtually no possibility of harming the subjects in any way. The study itself is a no or minimal risk study in nature involving no pollutant exposures". You further stated that human subjects were exposed to what you describe as a "safe material for human inhalation". The fact of the matter is that the nature and magnitude of any risk to the subjects has yet to be determined. But risk to the subjects was not the basis for Dr. Birnbaum's proposed disciplinary action. The fact remains that by increasing the study dosage you conducted an exposure not approved by the IRB nor consented to by the subjects who participated in this research. You also failed to fulfill the requirement and your obligation to ensure that the consent forms were properly signed, again deviating from the human study protocols approved by the Institutional Review Board (IRB).

I cannot over emphasize the importance of adhering strictly to medical and research protocols. This is of the utmost importance when doing human subject testing. The subjects enter into a participation agreement based on the information they obtain during the screening process. Any changes to the research project's protocol, especially without informing the subjects and obtaining their consent to continuing their participation, is an extreme breach of faith and is medically and scientifically irresponsible. In that regard, I find that the charge, "disregard of a directive (Federal regulation) - EPA Order 1000.17, Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research" is sustained.

In determining the penalty to be imposed for this sustained charge I have considered the applicable aggravating and/or mitigating factors.

There are several aggravating factors that are applicable in this case. The first is that as a senior principal investigator and national and world expert, *you are obligated* to follow applicable guidelines and protocols that are in place to protect human subjects and minimize the possibility of liability to the Government. EPA Order 1000.17, Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research, is the rule of law for conducting human research in the EPA. *Any* changes to research protocols already approved by the IRB must be re-submitted to them for approval before the change may take place. You were well aware of this requirement as evidenced by your admission both in your oral and written replies. Moreover, in our face-to-face meeting, you admitted to being aware of the deviation which would be expected given your substantial expertise and familiarity with this line of research. Secondly, this is not the first time that you have been guilty of violating protocols. You were made aware of the prior incident in which you deviated from the study's protocol. You were admonished by a memorandum dated December 18, 1997, by your previous supervisor, Dr. Robert Devlin. Particularly aggravating is the fact that then, as now, you have never expressed any regret, admitted to any wrong doing, unintentional or otherwise, or indicated in any way that

Kim

November 6, 2001

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what you did was a breach of well-established, valid research standards, even after acknowledging that errors had been made. As worrisome as it is that you violated the protocols and standards of good research, I remain concerned and disappointed that you still do not seem to understand the significance of your actions.

The mitigating factors include the fact that you are a renowned senior research expert and have been truly dedicated in advancing the science in the field of aerosol exposures. As such, the Agency has recognized your accomplishments in the past and again, recently with Scientific and Technology Achievement Awards at Levels II and III. Additionally, other than this particular issue, you have had no past disciplinary actions; are dependable; get along with fellow workers; and show the potential to be able to put this event behind you and move on to other achievements. Therefore, in consideration of all relevant factors, I am mitigating the proposed twenty-one (21) day suspension to a seven (7) calendar day suspension. I believe that this seven day suspension will promote the efficiency of the service and will serve as a deterrent to future violations. Accordingly, you will be suspended for seven (7) calendar days beginning January 2, 2002 and ending January 8, 2002. You are to report for duty at your regularly scheduled time of arrival on January 9, 2002. I have delayed this start date to allow adequate time for you to thoroughly review and provide accurate dose information on each subject so as to expedite any decisions regarding subject follow up. This task should be given priority over any other work you may have scheduled at this time. Following your return to work, you are to adhere to all study protocols, including established procedures for requesting changes. You are advised that future offenses of this nature will not be tolerated and will result in more severe disciplinary action, up to and including your possible removal from EPA employment.

You may contest this action through the negotiated grievance procedure contained in Article 43 of the Master Collective Bargaining Agreement between the United States Environmental Protection Agency and the American Federation of Government Employees.

You are asked to sign and date the acknowledgment copy of this letter. Your signature does not indicate agreement with the contents of this letter but merely indicates that you received it and any attachments thereof.

cc: Dr. Linda Birnbaum (MD-58A)
Dr. James Samet (MD-58D)
Mary S. Day (C639-02)

RECEIPT ACKNOWLEDGED:

Name

Date

1



OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

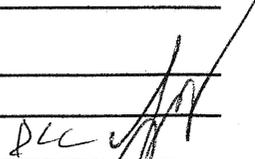
RECEIPT OF DOCUMENTS FROM REBECCA CALDERONE

On May 12, 2005, SA DAVID L. COTNER, Special Investigations Unit, received documents from Dr. REBECCA CALDERONE (919/966-0617), Director, Human Studies Division (HSD), EPA at the University of North Carolina (UNC) in her office, room number 152, at the EPA Human Studies Building, 104 Mason Farm Road, Chapel Hill, NC. CALDERONE was not shown identification as she was previously known to reporting agent. The purpose of the receipt of documents was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

The documents received from CALDERONE included two reports submitted by Dr. FRED MILLER. The first was titled IRB# 91-EPA-226 Determination of Deposition Dose of Inhaled Particles in Human Lungs, Review of Expected Mass Deposited and Potential Risk to Subjects, dated September 11, 2001 (Attachment 1). The second was titled Assessment of Potential Maximum Dose in ADEPOSIT Subjects, dated March 15, 2002 (Attachment 2). CALDERONE also provided a copy of the Annual Update on HSD Human Subjects Progressive Action Plan, dated July 9, 2004 (Attachment 3).

CALDERONE provided a memorandum dated April 4, 2002 from Dr. ROBERT DEVLIN, titled Exposure of Subjects to Sebacate Particles in ADEPOSIT (Attachment 4). The memorandum referred to a study by P. Brand, et. al, titled Total Deposition of Therapeutic Particles During Spontaneous and Controlled Inhalations (Attachment 5). The memorandum summarized the Brand study and stated the Brand paper had subjects who 'were exposed to a particle concentration of 260 mg/m(cubed) and there were no reported adverse health effects associated with the study. Dr. Kim's subjects were exposed to a maximum particle concentration of 150 mg/m (cubed) with no reported adverse health effects. Assuming subjects in both studies were using the same breathing pattern, Dr. Kim's subjects inhaled only 58% as much particle mass as the subjects in the Brand study.'

Calderone also provided two memorandums given to Dr. CHONG KIM which ultimately gave

Investigation Conducted on: May 12, 2005	Conducted at: Chapel Hill, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 12, 2005	Prepared by: SA David L. Cotner 

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EPA Form 2720-15 (Computer)

him a seven day suspension. A Notice of Proposed Suspension, dated October 3, 2001 (Attachment 6) from Dr. LINDA BIRNBAUM proposed a 21-day suspension of KIM. A Notice of Decision to Suspend, dated November 6, 2001 (Attachment 7) from Dr. HAROLD ZENICK suspended KIM for seven days from January 2 - January 8, 2002. The memorandum also referred to a September 24, 2001 memorandum from BIRNBAUM to KIM that indefinitely banned KIM from conducting human studies.

Attachments

1. Review of Expected Mass Deposited & Potential Risk to Subjects, dated September 11, 2001
2. Assessment of Potential Maximum Dose in ADEPOSIT Subjects, dated March 15, 2002
3. Annual Update on HSD Human Subjects Progressive Action Plan, dated July 9, 2004
4. Memorandum dated April 4, 2002 from Dr. ROBERT DEVLIN
5. Study by P. Brand, et. al, titled Total Deposition of Therapeutic Particles During Spontaneous and Controlled Inhalations
6. Notice of Proposed Suspension, dated October 3, 2001
7. Notice of Decision to Suspend, dated November 6, 2001

CONFIDENTIAL

IRB# 91-EPA-226 Determination of Deposition Dose
of Inhaled Particles in Human Lungs

Review of Expected Mass Deposited
and
Potential for Risk to Subjects

Submitted to

Dr. Linda S. Birnbaum
Director, Human Studies Division
U.S. Environmental Protection Agency
Chapel Hill, NC 27599

Submitted by

Dr. Frederick J. Miller
CIIT Centers for Health Research
Research Triangle Park, NC 27709

Dr. Bahman Asgharian
CIIT Centers for Health Research
Research Triangle Park, NC 27709

September 11, 2001

Attachment (1)

the same subjects will be encouraged to participate in both studies. For polydisperse aerosols (POLYDEPO), lung deposition will be measured for six different size aerosols on the same day. Subjects will make two visits to complete the study." One can not tell from this statement if, for example, in the polydisperse protocol does Visit 1 include all particle sizes and σ_g s for the fixed tidal volume of 500 ml or does it include all particle sizes and tidal volumes for a fixed σ_g ? The way the protocol is written there is no way to discern which was done.

Dosimetry Model Used for Calculations

There are a number of anatomical models of the human lung available in the literature. The model of Weibel (1963) is a typical path lung model based upon some measurements and some extrapolations of calculated values. A typical path model based upon more extensive measurements of the human lung was developed by Yeh and Schum (1980). Yeh and Schum also developed a typical path lobar-specific model for humans. The detailed lung cast measurements of the human lung made by Raabe and coworkers (1976) have been used by Hofmann, Koblinger and colleagues to develop stochastic lung models (Koblinger and Hofmann, 1985, 1988, 1990; Hofmann and Koblinger, 1990, 1992). In the stochastic modeling of lung deposition, Monte Carlo methods are employed that exploit the statistical distributions of the morphometric data on diameters, lengths, branching and gravity angles for individual airway generations, as well as correlations between daughter and parent airways in major and minor daughter airways. The human model used for the deposition computations presented in this review are based upon the recently published stochastic, multiple-path model of the human lung developed by Asgharian et al. (2001). This model is the most advanced dosimetry model currently available for calculating deposition in specific lobes and individual paths and makes the most extensive use of available biological and statistical data on lung geometry. Since there are toxicological data available on DEHS from a rat inhalation study, computations were also made for the delivered dose to rats of DEHS. For these calculations, the multiple path model of particle deposition in the rat lung of Anjilvel and Asgharian (1995) was used.

Assumptions for Worst Case Calculations

The lack of specificity in the protocol required us to invoke the following assumptions:

- For ultrafine particles, all concentrations were assumed to be derived from 80,000 particles per cm^3 .

Using the worst case assumptions described earlier, Tables 3 and 4 provide the calculated delivered dose of DEHS for the monodisperse aerosol exposure studies. As can be seen from Table 3, the ultrafine particulate studies result in a negligible mass deposited in the TB region (0.895 to 1.07 μg) and in the P region (1.51 to 2.27 μg), even if all of the particle sizes and tidal volumes were studied on the same day. As Table 4 demonstrates, negligible deposition in the tracheobronchial and pulmonary regions also occurs for the 1- μm diameter DEHS particle. For this particle size, TB deposition in small and large lungs ranges from about 241–246 μg while pulmonary deposition ranges from 277–523 μg . Moreover, these burdens arise if all exposure scenarios involving 1- μm particles were conducted on the same day.

The same can not be said for the coarse mode particles studied. Depending upon the specific breathing frequency, tidal volume, and particle size (3 μm or 5 μm) used in a given exposure, tracheobronchial deposition can vary from about 0.15 mg to more than 6 mg while pulmonary deposition varies between 0.057 mg and 6.79 mg (see Table 4). It is important to note that these calculations arise from using the worst case assumptions stated earlier. After a quality assurance (QA) audit of the raw data, a table can be constructed for the exact number of breaths each subject used in a particular exposure combination, the number of particle sizes and tidal volumes administered on a given day, and the time interval between potential return visits. Given this information more accurate estimates of dose can be calculated using deposition fractions in Tables 1 and 2 and other pertinent information. Alternatively, the deposition mass can be adjusted by division of the product of any factors that were overestimated (e.g., if 10 breaths were used then the deposition masses appearing in our tables would need to be divided by 2; if the number of particles per cm^3 are less than those that were assumed for these calculations, then the deposition mass can be altered by the ratio of the assumed to the actual number).

If the eight combinations of breathing frequency and tidal volume were all studied on the same day, the mass of 5- μm particles deposited in the TB region would range from 20.3–22.4 mg. Pulmonary region deposited mass would range from about 15–25 mg. We feel certain that fewer breaths than 20 were used by most subjects and that the number concentration was probably not 10,000 particles per cm^3 as stated in the protocol, both of which would drastically reduce the deposited mass of DEHS particles. *Our reason for feeling that actual exposures may have been much less stems from a sentence in supplemental information we received after we had made our calculations. In a memo from Dr. Chong Kim to Dr. Linda Birnbaum dated August 20, 2001, the following statement is made "...During the test, they used a portable aerosol*

acute lung injury. These investigators found that a dose of 3.75-mg DEHS/100 g body weight caused negligible acute pulmonary toxicity. In the discussion section of the Brain et al. study, they compared the toxicity they saw with equivalent high doses of metal oxides. The metal oxides produce significant changes in some of the parameters that were measured, but DEHS produced minimal changes. Far lower doses of toxic materials produce effects on PMNs and other end points that are greater than DEHS causes by a factor of around 40. Among the animal toxicological studies, the study by Rubin et al. (1983), which was presented at the annual meeting of the Society of Toxicology but never published in a journal, stands out because these investigators used an inhalation model. Rats were exposed to DEHS aerosol (0.9- μ m mass median diameter) at exposure doses up to 250 mg/m³ for four hours per day, five days per week for seven weeks. Using the multiple-path dosimetry model of Anjilvel and Asgharian (1995) for the rat, we modeled the deposition and clearance of DEHS associated with the Rubin et al. (1983) study. At the end of the first week of exposure, the alveolar mass retained was about 17 mg. Over the 7-week exposure period, the alveolar mass rose to approximately 20 mg. TB mass retention never exceeded 0.048 mg during the course of the study. In their study, Rubin and colleagues noted only slight changes in the lung pressure-volume curve, and there were no alterations in pulmonary macrophage or liver function. Thus, while 250 mg/m³ is an astronomically high level of exposure, the resultant toxicity was minimal. Based on studies using healthy hamsters and rats, one may infer that DEHS is of minimal toxicity to healthy subjects even at high exposure levels.

Potential Risk to Human Subjects Studied in IRB# 91-EPA-226

While there is no question that the human subjects involved in this study had deposited masses in the pulmonary and tracheobronchial regions far greater than the 50 μ g stated in the protocol, the real issue is how high was the deposited dose and was there an associated potential risk. To answer this question, we need to examine potential consequences for each of the five study groups.

Two of the five groups studied were classified as "young normals" and "old normals." From the toxicity data and the relative comparison of dose between animals and humans, it is very unlikely that doses on the order of several milligrams would provide any toxicity to healthy subjects. This point is articulated well in the discussion section of the Brain et al. (1996) paper, where the authors note that the dose they used in their hamster studies would be the equivalent to 37.5 mg/kg. Given the average body weight of 50–70 kg in female and male human subjects, respectively, an extremely large deposited mass would have minimal risk for acute toxicity.

Not only do COPD individuals have increased deposition relative to normal subjects, their ability to clear particles is relatively poor. Thus, even if acute responses were not invoked, one can not categorically rule out, depending upon the actual doses delivered, that COPD individuals may have had potential for adverse responses subsequent to their participation in the studies.

We would strongly suggest that a small, independent group (perhaps one person each from the areas of epidemiology, clinical pulmonary, and dosimetry modeling) be brought in to examine the potential for risk in the various subjects used in this study after it has been clearly established what the actual doses received by the subjects were. While our inference must be speculative due to the protocol not containing enough specifics to calculate accurately the dose of DEHS deposited, the presence of a tolerance distribution in the human population allows for the potential for some responses in more sensitive individuals. While DEHS has been used in deposition studies, the magnitude and number of exposures were small compared to those that could be calculated from the numbers presented in the protocol. The real issues remains clearly establishing what the actual exposures were and then having an assessment of the potential for risk and making modifications to any future protocols that ensure lower DEHS exposure levels are used.

Recommended Path Forward

- Conduct a QA audit of the study records to establish the following information for each subject.
 - The exact nature of the exposure combinations (i.e., what particle sizes, flow rates, tidal volumes) done on a given day and the number of breaths the subject took for each exposure combination.
 - The interval of time between daily visits if the subject participated in more than one study (ADEPOSIT, SDEPOSIT, POLYDEPO) or returned on separate occasions in any given study.
- The QA audit should at a minimum focus on all persons exposed to 3- μ m or 5- μ m monodisperse particles in the nonbolus regimen. The next priority would be an audit of the records for persons exposed to the 3- μ m aerosol in the POLYDEPO study.
- Once the complete exposure scenario information is tabulated for subjects, calculate the predicted mass of DEHS particles deposited in the TB and P regions for each exposure scenario and add them together if more than one scenario was used for a subject on a given day.

0.06	1	30	1000	0.101	0.221	0.118	0.177
0.08	1	7.5	500	0.116	0.323	0.137	0.117
0.08	1	15	500	0.098	0.245	0.112	0.089
0.08	1	30	500	0.089	0.177	0.097	0.065
0.08	1	60	500	0.089	0.123	0.092	0.045
0.08	1	3.75	1000	0.122	0.417	0.162	0.308
0.08	1	7.5	1000	0.103	0.323	0.131	0.253
0.08	1	15	1000	0.094	0.236	0.112	0.193
0.08	1	30	1000	0.093	0.166	0.105	0.140
0.1	1	7.5	500	0.100	0.279	0.118	0.101
0.1	1	15	500	0.087	0.205	0.098	0.075
0.1	1	30	500	0.082	0.144	0.088	0.053
0.1	1	60	500	0.084	0.099	0.086	0.036
0.1	1	3.75	1000	0.106	0.364	0.139	0.279
0.1	1	7.5	1000	0.092	0.272	0.114	0.220
0.1	1	15	1000	0.086	0.194	0.101	0.162
0.1	1	30	1000	0.088	0.134	0.097	0.115

Table 2. Monodisperse Particle Exposures: Fine and Coarse Deposition Fractions

Particle Characteristics		Breathing Parameters		Deposition Fraction			
Diameter (μm)	σ_g	BF	Tidal Vol. (ml)	(Small Lung)		(Large Lung)	
				TB	P	TB	P
1	1	7.5	500	0.061	0.160	0.076	0.060
1	1	15	500	0.061	0.095	0.067	0.035
1	1	30	500	0.067	0.056	0.067	0.020
1	1	60	500	0.081	0.034	0.075	0.012
1	1	3.75	1000	0.065	0.227	0.089	0.210
1	1	7.5	1000	0.118	0.474	0.076	0.132
1	1	15	1000	0.070	0.080	0.074	0.079
1	1	30	1000	0.083	0.048	0.081	0.046
3	1	7.5	500	0.129	0.455	0.210	0.160
3	1	15	500	0.107	0.337	0.146	0.125
3	1	30	500	0.132	0.224	0.117	0.080
3	1	60	500	0.270	0.113	0.122	0.046
3	1	3.75	1000	0.148	0.581	0.256	0.358
3	1	7.5	1000	0.118	0.474	0.173	0.346
3	1	15	1000	0.133	0.315	0.134	0.269
3	1	30	1000	0.259	0.165	0.133	0.173
5	1	7.5	500	0.249	0.480	0.388	0.135

0.08	1	30	500	1.91E-05	3.80E-05	2.08E-05	1.39E-05
0.08	1	60	500	1.91E-05	2.64E-05	1.97E-05	9.65E-06
0.08	1	3.75	1000	5.23E-05	1.79E-04	6.95E-05	1.32E-04
0.08	1	7.5	1000	4.42E-05	1.39E-04	5.62E-05	1.09E-04
0.08	1	15	1000	4.03E-05	1.01E-04	4.80E-05	8.28E-05
0.08	1	30	1000	3.99E-05	7.12E-05	4.50E-05	6.01E-05
0.1	1	7.5	500	4.19E-05	1.17E-04	4.94E-05	4.23E-05
0.1	1	15	500	3.64E-05	8.59E-05	4.11E-05	3.14E-05
0.1	1	30	500	3.43E-05	6.03E-05	3.69E-05	2.22E-05
0.1	1	60	500	3.52E-05	4.15E-05	3.60E-05	1.51E-05
0.1	1	3.75	1000	8.88E-05	3.05E-04	1.16E-04	2.34E-04
0.1	1	7.5	1000	7.71E-05	2.28E-04	9.55E-05	1.84E-04
0.1	1	15	1000	7.20E-05	1.63E-04	8.46E-05	1.36E-04
0.1	1	30	1000	7.37E-05	1.12E-04	8.13E-05	9.63E-05
			Mass deposited	8.95E-04	2.27E-03	1.07E-03	1.51E-03
			Thoracic deposition	3.17E-03		2.58E-03	

Table 4. Monodisperse Particle Exposures: Fine and Coarse Deposited Mass

Particle Characteristics		Breathing Parameters		Deposition (mg)			
Diameter (μm)	σ_g	BF	Tidal Vol. (ml)	(Small Lung)		(Large Lung)	
				TB	P	TB	P
1	1	7.5	500	0.0160	0.0418	0.0199	0.0157
1	1	15	500	0.0159	0.0248	0.0175	0.0091
1	1	30	500	0.0175	0.0146	0.0175	0.0052
1	1	60	500	0.0211	0.0088	0.0195	0.0031
1	1	3.75	1000	0.0340	0.1187	0.0466	0.1099
1	1	7.5	1000	0.0617	0.2478	0.0397	0.0690
1	1	15	1000	0.0365	0.0418	0.0386	0.0412
1	1	30	1000	0.0432	0.0250	0.0422	0.0240
			Mass Deposited	0.2459	0.5233	0.2415	0.2772
3	1	7.5	500	0.1781	0.6281	0.2899	0.2209
3	1	15	500	0.1450	0.4567	0.1978	0.1694
3	1	30	500	0.1732	0.2939	0.1535	0.1050
3	1	60	500	0.3353	0.1403	0.1515	0.0571
3	1	3.75	1000	0.4103	1.6107	0.7097	0.9925
3	1	7.5	1000	0.3222	1.2941	0.4723	0.9447
3	1	15	1000	0.3535	0.8373	0.3562	0.7150
3	1	30	1000	0.6573	0.4187	0.3375	0.4390
			Mass Deposited	2.5749	5.6798	2.6684	3.6436

1	3	1.5	15	500	0.175	0.121
1	0.1	1.5	15	1000	0.105	0.168
1	1	1.5	15	1000	0.079	0.096
1	3	1.5	15	1000	0.163	0.262
2	0.1	2.5	15	500	0.124	0.081
2	1	2.5	15	500	0.101	0.059
2	3	2.5	15	500	0.244	0.094
2	0.1	2.5	15	1000	0.124	0.179
2	1	2.5	15	1000	0.105	0.130
2	3	2.5	15	1000	0.238	0.207

Table 6. Polydisperse Aerosol Exposures: Deposited Mass

A. Small Lung

Visit	Particle Characteristics		Breathing Parameters		Deposition (mg)	
	MMAD (μm)	σ_g	BF	Tidal Vol. (ml)	TB	P
1	0.1	1.5	15	500	3.81E-05	9.05E-05
1	1	1.5	15	500	1.68E-02	3.16E-02
1	3	1.5	15	500	1.84E-01	4.56E-01
1	0.1	1.5	15	1000	7.46E-05	1.77E-04
1	1	1.5	15	1000	3.81E-02	5.63E-02
1	3	1.5	15	1000	4.86E-01	8.03E-01
				Mass deposited	0.7250	1.3473
				Thoracic deposition	2.0724	
2	0.1	2.5	15	500	4.57E-05	9.72E-05
2	1	2.5	15	500	2.33E-02	4.30E-02
2	3	2.5	15	500	2.80E-01	3.49E-01
2	0.1	2.5	15	1000	8.63E-05	1.99E-04
2	1	2.5	15	1000	5.82E-02	7.40E-02
2	3	2.5	15	1000	7.85E-01	5.29E-01
				Mass deposited	1.1465	0.9955
				Thoracic deposition	2.1419	

B. Large Lung

	Particle Characteristics	Breathing Parameters	Deposition (mg)
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CONFIDENTIAL

Assessment of Potential Maximum Dose in ADEPOSIT Subjects

Submitted to

Dr. James Samet
U. S. Environmental Protection Agency
58 D U.S. EPA Mailroom, Research Triangle Park, NC

Submitted by

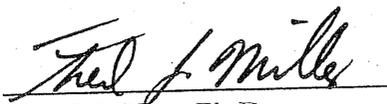
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Bahman Asgharian, Ph.D.
Analysis Team Leader

3-15-02

Date



Fred J. Miller, Ph.D.
Vice President for Research

3/15/02

Date

Objective

An independent study was conducted at CIIT Centers for Health Research to assess the dose received by 2 subjects (A21 & C05) in the protocol IRB#91-EPA 226 during a brief exposure to di (2-ethylhexyl) sebacate (DEHS) particles. These subjects corresponded to typical cases among asthmatic and chronic obstructive pulmonary disease (COPD) patient groups with the greatest potential risk for adverse effects as a result of exposure to the airborne materials.

Approach

The deposition calculations were carried out using the multiple-path lung deposition model of Anjilvel and Asgharian (1995). There are no lung morphometry measurements currently available on individuals with asthma or COPD. For the current analyses, the lung geometry of normal, healthy adults was used in the calculations since study subjects were only mildly diseased. Two adult human lung geometries with asymmetric branching structures in the tracheobronchial region (TB) were generated. The generated lung structures were based on the morphometric measurements of Raabe et al. (1976). Each lung consisted of a stochastically generated asymmetric branching structure in the TB region (Koblinger and Hofmann, 1990; Asgharian et al., 2001) completed by attaching an 8-generation symmetrical acinus (Yeh et al., 1979) to the end of the terminal bronchioles. These two lungs were selected from a pool of 30 stochastically generated lungs and represented limiting cases of the lungs with the smallest and largest number of TB airways. Incorporating the asymmetric feature of the lung structure allowed for more realistic assessment of the site-specific and local deposition of particles in the respiratory tract.

Subject Input Data

Various inputs such as the subject's lung parameters (e.g. functional residual capacity, head volume etc.) and breathing parameters (tidal volume, and breathing frequency) were necessary to perform the calculations. To obtain these data and to ensure that CIIT understood the manner in which Dr. Kim's study was conducted, a meeting was held with Drs. C. S. Kim, J. Samet, and B. Asgharian on Monday, March 4, 2002. The exposure

data and other necessary information were obtained to enable the CIIT team to calculate the dose received by these 2 individuals.

Dr. Kim stated that these 2 subjects were exposed orally for one day only to 5 μm -diameter monodisperse particles of mass density 0.89 g/cm^3 at a concentration of 50 mg/m^3 . The subjects did not return for any additional exposures. The highest dose to an individual was therefore at the end of the exposure day when there was no appreciable clearance. The results calculated in the report were thus limited to the deposition mass only. The breathing parameters and the exposure concentrations were identical for the 2 subjects. Each subject was trained to inhale 4 different volumes of air at various breathing flow rates. The breathing frequencies were calculated and are provided in Table 1 along with the tidal volumes for each exposure scenario. While we used the functional residual capacity (FRC) values supplied by Dr. Kim, the value for FRC of 6.91 liters for subject C05 is, in our opinion, highly suspect for an individual with mild COPD and should be verified by Dr. Kim.

Each subject was exposed to 11 different breathing scenarios on the exposure day. The number of breaths varied for each exposure scenario. The information on the number of breath per exposure scenario was provided by Dr. Kim for one individual (A21) and an estimate was given for the other subject (C05). Due to lack of information, it was assumed that the inhalation and exhalation times were equal and there was no pause between inhalation and exhalation. Default parameter values available in the literature were used when the values were missing.

Deposition fraction during one breathing cycle via mouth breathing was calculated for the two lung geometries using the FRC, breathing and lung parameters of the subjects, and particle size characteristics. Total and regional mass deposited in the respiratory tract in the subjects was subsequently calculated for each breathing scenario from the expression given below.

Table 1. Breathing parameters of the subjects during the exposures as provided by Dr. Kim.^a

Tidal Volume (cm ³)	Breathing Period (s)	Breathing Frequency (min ⁻¹)
350	4	15.00
350	2.8	21.43
500	6.66	9.01
500	4	15.00
500	2	30.00
750	6	10.00
750	4	15.00
750	3	20.00
1000	8	7.50
1000	4	15.00
1000	2	30.00

^a The functional residual capacity values supplied by Dr. Kim for subjects A21 and C05 were 3.05 and 6.91 liters, respectively.

Table 3. Deposited mass of particles in subject A21 with FRC =3.05 liters using the lung geometry with the largest number of TB airways.

Number of Breaths	Deposition Fraction				Deposited Mass (mg)			
	Head	TB	PUL	Total	Head	TB	PUL	Total
8	0.373	0.233	0.114	0.72	0.052	0.033	0.016	0.101
11	0.457	0.198	0.105	0.759	0.088	0.038	0.020	0.146
8	0.26	0.302	0.217	0.78	0.052	0.060	0.043	0.156
11	0.36	0.233	0.223	0.816	0.099	0.064	0.061	0.224
10	0.492	0.214	0.17	0.875	0.123	0.054	0.043	0.219
8	0.273	0.26	0.331	0.865	0.082	0.078	0.099	0.260
11	0.342	0.227	0.319	0.888	0.141	0.094	0.132	0.366
10	0.388	0.228	0.289	0.905	0.146	0.086	0.108	0.339
6	0.228	0.276	0.386	0.891	0.068	0.083	0.116	0.267
7	0.329	0.235	0.357	0.921	0.115	0.082	0.125	0.322
7	0.359	0.41	0.192	0.961	0.126	0.144	0.067	0.336
Accumulated total mass (mg):					1.092	0.814	0.831	2.737

Table 5. Deposited mass of particles in subject C05 with FRC =6.91 liters using a lung geometry with the largest number of TB airways.

Number of Breaths	Deposition Fraction				Deposited Mass (mg)			
	Head	TB	PUL	Total	Head	TB	PUL	Total
9	0.479	0.149	0.002	0.63	0.075	0.023	0.000	0.099
9	0.568	0.122	0.002	0.693	0.089	0.019	0.000	0.109
6	0.366	0.277	0.032	0.675	0.055	0.042	0.005	0.101
11	0.496	0.208	0.03	0.734	0.136	0.057	0.008	0.202
10	0.653	0.153	0.021	0.827	0.163	0.038	0.005	0.207
8	0.384	0.282	0.133	0.799	0.115	0.085	0.040	0.240
11	0.478	0.227	0.128	0.833	0.197	0.094	0.053	0.344
9	0.542	0.201	0.116	0.859	0.183	0.068	0.039	0.290
6	0.312	0.317	0.211	0.841	0.094	0.095	0.063	0.252
7	0.453	0.223	0.209	0.884	0.159	0.078	0.073	0.309
6	0.573	0.208	0.147	0.929	0.172	0.062	0.044	0.279
Accumulated total mass (mg):					1.439	0.661	0.331	2.432

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

July 9, 2004

MEMORANDUM

SUBJECT: Annual Update on HSD Human Subjects Progressive Action Plan

FROM: Hal Zenick, Ph.D. 
Associate Director of Health, NHEERL (B105-01)

TO: Peter Preuss, Ph.D.
EPA Human Studies Research Review Official (8601D)

I am pleased to submit the Human Studies Division's Annual Update on HSD Human Subjects Progressive Action Plan (previously referred to as Corrective Action Plan). The Division continues to make significant progress in addressing, and exceeding, the recommendations provided by the external review panel in August 2002. NHEERL is committed to a continued, diligent pursuit of the highest ethical and safety standards and practices in the conduct of studies involving human subjects. We appreciate the support and advice provided by your office over the past year and look forward to a continued, close working relationship.

cc: Kevin Y. Teichman
John Jones
Rebecca L. Calderon
William F. McDonnell

Attachment (3)

The TRC exposure monitoring system and its oversight is state of the art and is being sustained. For the non-TRC exposures to environmental agents, an independent laboratory such as the UNC investigational drug pharmacy will provide, under contract, independent verification of concentrations of dosing solutions. An exception to this is the procedure for preparation of drug solutions (e.g. methacholine solutions for bronchial inhalation challenge testing) which are available prepackaged in USP grade and therefore of known purity, stability, and weight. These solutions will be prepared by two investigators/technicians following an acceptable standard operating procedure which has been approved by the HSD Quality Assurance Officer.

Recommendation 5: Each principal investigator must identify an acceptable range for delivered dose (or concentration of dosing solutions) for each protocol to more precisely determine when an incorrect dosing event has occurred.

Action: Protocols active in 2002 underwent a review, and all new protocols are reviewed to insure that ranges of acceptable exposure (dose) are provided rather than just the target dose. This is reviewed by the branch chief early in the development of the protocol and again later by the division director, division QA officer, and the Director of the NHEERL Human Research Protocol Office.

Recommendation 6: Measures of delivered dose should be included in all active protocols, whether or not the delivered dose is the parameter of concern.

Action: This has been included for all protocols approved since 2002.

Recommendation 7: Periodic re-review and audit of clinical studies to proactively identify and correct any problems, as well as improve study protocols should be undertaken.

Action: Ongoing clinical studies may be reviewed or audited by a team of QA experts and/or by the NHEERL Human Research Protocol Office.

Protocol Office File Review: We are currently reviewing files of all protocols contained in the NHEERL Protocol Office. Records of completed/closed studies are being archived. Files of all active studies are being reviewed for the presence of an EPA approval letter for the conduct of human research. Files of active studies conducted in an NHEERL facility and for which the UNC IRB is the IRB of record are also being reviewed for the presence of a current IRB approval. Files of active studies conducted off-site and for which the primary IRB is at another institution are also being reviewed for an original IRB approval. A tracking system will be implemented later in 2004 to allow ongoing tracking of current IRB approval for all active studies.

Protocol Office Technical Review: We will consider implementing a system for periodically auditing the performance of selected studies in 2005. This review might include such elements as observation of acquisition of informed consent,

Action: This has been done.

Recommendation 13: Add more complete investigator and subject certification statements.

Action: This is being done consistent with the guidelines of our IRB.

Recommendation 14: Consent forms should list all investigators and their phone numbers and a 24-hour contact number.

All investigators are listed on the consent forms, and the phone number of the Principal Investigator, the Director of the NHEERL Human Research Protocol Office, and the Head of the UNC IRB are listed. We do not believe that there is a need to list the phone numbers of other investigators. A toll-free telephone number with an answering machine will be provided for participants to request a return call concerning a study in which they are participating. For studies in which medical issues might reasonably be expected to arise (e.g. fever several hours after the performance of a bronchoalveolar lavage), the PI will ensure that a physician will be on-call 24 hours per day for an appropriate period following the procedure.

Recommendation 15: A designated institutional official should be provided with copies of all pertinent IRB meeting minutes.

The Director of the NHEERL Human Research Protocol Office receives those minutes from the UNC IRB.

IV. Training, Mentoring, and Development of a Culture of Safety

Recommendation 16: Simulations or dry-run exercises with appropriate levels of physical or psychological fidelity should be undertaken as a technique for training and assessing new quality control processes or rapid-pressured decision-making responses to potential subject complications.

Action: Field studies conduct extensive training of field staff and usually run a limited number of subjects to assure that procedures can be implemented as designed. Simulations or dry-runs are required when appropriate for controlled exposure studies using new methods or exposure protocols. The HSD medical staff routinely conduct "code" drills to practice emergency techniques.

Recommendation 17: HSD should establish a safety culture to ensure that a concern for safety is actively maintained on an ongoing basis. Bring in safety experts as speakers or seminar leaders from related disciplines, institute a speaker series.

Action: This has been slowly implemented with presentations by Dr. Kerm Henricksen in December 2002 and with a presentation/workshop by Dr. Dan Nelson, head of the

Action:

This is a division management activity with participation by appropriate NHEERL human research ethics personnel, and improvements in this area are under consideration. Currently branch chiefs hold regular meetings with post-docs, and the HSD division director meets at least once per year with the post-docs. The Director of the NHEERL Human Research Protocol Office gave a talk on human research to the NHEERL Training Organization in June 2004. Investigators without prior human study experience will not be allowed to be the PI of a study; they must first serve as a co-PI under the mentorship of an experienced PI.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
RESEARCH TRIANGLE PARK, NC 27711

April 4, 2002

MEMORANDUM

SUBJECT: Exposure of Subjects to Sebacate Particles in ADEPOSIT

FROM: Robert Devlin, Chief *R. Devlin*
Clinical Research Branch

TO: John Vandenberg, Acting Director
Human Studies Division

Dr. Kim was asked to calculate the maximum dose of 5 micron particles delivered to each of the subjects in his study. His calculations are appended to this letter as "Estimation of maximum dose of ADEPOSIT subjects." The maximum dose varied from 0.89 – 2.69 mg. To validate the approach taken by Dr. Kim in arriving at these calculations, two outside dosimetry experts from CIIT were asked to perform an independent analysis on data provided for two subjects, who represent a "typical" subject and one with the greatest potential risk for adverse effects as a result of exposure to airborne materials (a subject with COPD). The calculations were carried out using the model of Anjilvel and Asgharian (1995) and attached to this letter as "Assessment of Potential Maximum Dose in ADEPOSIT Subjects." Their report concludes that the approach taken by Dr. Kim was valid.

Note that three different size particles were used in this study. These calculations were performed on exposures in which the largest size particles (5 microns) were used, since that would result in the largest mass of particles delivered to the lung. However, some subjects were exposed to 3 micron and 1 micron particles, in addition to 5 micron particles. These exposures were separated by a few days or up to a few weeks. Taking into account clearance of particles after each exposure, Dr. Kim has calculated that the additional particle dose delivered to these subjects may be estimated by multiplying the dose received with 5 micron particles by 1.3. A copy of his e mail explaining these calculations is appended to this letter.

Dr. Bennett, a researcher at UNC who is an expert in human dosimetry, was asked to compare the dose received by Dr. Kim's subjects to that received by humans in other dosimetry studies. After reading several papers in which humans were exposed to the same kind of particles as used in Dr. Kim's study, Dr. Bennett was unable to make a direct comparison – primarily because the papers did not contain sufficient details (such as the number of breaths of particles each subject

inhaled) to allow a calculation of total dose delivered. However, he was able to calculate the concentration of 1, 3, 5 micron particles used in those studies. One such paper is attached to this letter (Brand et al., 1999). In this paper subjects were exposed to a particle concentration of 260 mg/m³ and there were no reported adverse health effects associated with the study. Dr. Kim's subjects were exposed to a maximum particle concentration of 150 mg/m³ with no reported adverse health effects. Assuming subjects in both studies were using the same breathing pattern, Dr. Kim's subjects inhaled only 58% as much particle mass as the subjects in the Brand study.

Maximum dose estimation for ADEPOSIT subjects

Normal subjects		Elderly subjects		Asthmatic subjects		COPD subjects	
Subj #	Dose (mg)	Subj #	Dose (mg)	Subj #	Dose (mg)	Subj #	Dose (mg)
N01	1.78	E03	1.90	A01	1.20	C01	2.64
N02*	1.00	E04	1.69	A02	1.10	C02	2.25
N03	1.91	E05	1.86	A03	1.17	C03	2.55
N05	2.15	E06	1.63	A04	1.06	C04	2.69
N06	1.91	E07	1.52	A05	1.04	C05	2.39
N08	1.87	E08	1.76	A06	0.89	C06	2.17
N09	2.28	E09	1.51	A07	0.97		
N11	2.23	E10	1.47	A08	1.94		
N12	2.27	E11	2.10	A09	2.40		
N13	2.04	E12	1.61	A10	2.15		
N14	2.00	E13	2.06	A11	2.17		
N15	2.08	E14	1.93	A12	2.19		
N17	2.13	E15	2.02	A13*	0.70		
		E16	1.65	A14*	0.10		
		E17	1.93	A15	2.29		
		E18	1.76	A16	2.22		
		E19	2.13	A17*	0.72		
				A19	2.24		
				A20	2.16		
				A21	1.85		
Highest	2.28	2.13		2.40		2.69	
Lowest	1.00	1.51		0.10		2.17	
Mean	1.97	1.79		1.53		2.45	

* Partial study

Total Deposition of Therapeutic Particles During Spontaneous and Controlled Inhalations

P. BRAND, I. FRIEMEL, T. MEYER, H. SCHULZ, J. HEYDER, K. HÄUBINGER

Clinical Research Group "Aerosols in Medicine" of the GSF-Institute for Inhalation Biology and the Clinic for Respiratory Medicine, Robert-Koch-Allee 6, D-82131 Gauting, Germany

Received 1 February 1999; revised 10 January 2000; accepted 10 December 1999

ABSTRACT: Treatment of systemic diseases by means of the inhalation route is hampered by uncertainties of the drug dose applied by inhalation. In this study, the hypothesis was tested that by standardization of the breathing maneuver used for inhalation, the interindividual variability of the dose deposited intrathoracically can be reduced. Therefore, breathing pattern during routine inhalations with jet nebulizers was measured in 18 patients with lung disease. Using monodisperse 3 μm particles, total deposition was then assessed for the measured spontaneous and for three controlled, slow breathing patterns. Particle deposition for the three controlled breathing patterns was additionally measured in 14 healthy subjects. The study has shown that within the study population the inhaled air volume and flow rate were quite different. Consequently, total particle deposition varied between 20 and 95%, depending on breathing pattern. For controlled, slow breathing patterns, deposition was on average higher, intersubject variability of deposition was smaller, and differences in deposition between healthy subjects and patients were negligible. Therefore, to perform efficient systemic treatment with aerosolized drugs, controlled, slow breathing patterns should be used. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association *J Pharm Sci* 89: 724–731, 2000

Keywords: particle deposition; variability; breathing pattern

INTRODUCTION

For many decades it has been well known that drugs for systemic therapy may be administered by means of the lungs. Since 1925, it has been known that inhaled insulin decreases the blood glucose level.¹ Nowadays, despite considerable progress in nebulizer technique and increased knowledge about particle deposition in the lung and drug absorption from lung surfaces, insulin administration by means of the lung is still not established but has reached a state of advanced clinical studies. The main reason for this slow-

ness of progress is related to uncertainties in the dose of drug administered by the inhalation route. The dose depends on many factors that are difficult to control: particle deposition in the lungs strongly depends on particle size, lung structure, and breathing pattern, with the result that particle deposition and thus the deposited dose varies considerably among patients.

In this study the hypothesis was tested that standardizing the breathing pattern decreases the intersubject variability of the dose deposited intrathoracically during inhalations of therapeutic particles generated with jet nebulizers. Therefore, in 18 patients deposition of inhaled monodisperse inert test particles was measured for the breathing pattern they used during routine inhalations with jet nebulizers and for three standardized patterns. In addition, particle deposition was

Correspondence to: P. Brand, (E-mail: brand@gsf.de)

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measured in 14 healthy subject for these standardized patterns.

METHODS

Subjects

Eighteen patients, 12 men and 6 women, who were used to aerosol therapy with jet nebulizers and 14 healthy subjects, 8 men and 6 women, participated in this study (Table 1). Eight patients had chronic obstructive pulmonary disease, seven patients had bronchial asthma, one patient had bronchiectasis, one patient had silicosis, and one patient had primary ciliary dyskinesia. Conventional pulmonary function tests were performed by use of a Jäger-Masterlab (Erich Jaeger GmbH, Würzburg, Germany). Relative values of the lung function parameters (%pred) were calculated as proposed by the European Community for Coal and Steel.² Informed written consent was obtained from each subject. The study protocol was approved by the Ethics Committee of the Medical School of the Ludwig-Maximilians-University (Munich, Germany).

Spontaneous Breathing Patterns

The breathing pattern of patients during routine inhalations with jet nebulizers (Pari-LC+ nebulizers, Pari GmbH, Starnberg, Germany, pressure 0.17 M Pa) was measured as follows: An ultrasonic transient-time flowmeter (TUBA, GHG AG, Zürich, Switzerland) was connected to the Venturi channel (air inlet) of the nebulizer. The analogous flow signal was recorded by a personal computer (Intel 386 CPU) with a analog-digital converter (Data Translation DT2821), and the flow rate through the nebulizer nozzle was added. This air flow through the nebulizer nozzle was

measured for each nebulizer before inhalation. All patients were instructed to perform inhalations as usual until 2.5 mL of a salbutamol inhalation solution (GlaxoWellcome, 1.5 mg salbutamol sulphate in isotonic NaCl solution) was completely nebulized. From the recorded flow rates of each breath the average spontaneous tidal volume, V_T , and flow rate, Q_i , were calculated for each patient.

Deposition

To measure total deposition of aerosol for various breathing patterns, a monodisperse inert test aerosol consisting of di-2-ethylhexyl sebacate (DEHS) droplets was used. Deposition measurements were performed using a device in which a laser aerosol photometer³ is combined with an piston-type ventilator, allowing the subject to inhale particles at controlled breathing patterns (Fig. 1). The ventilator has a volume of 2 L and is driven by a computer-controlled step motor. A system of computer-controlled magnetic valves allows us to connect the ventilator to ambient air, to an aerosol supply, or to a mouthpiece at which the subject wearing a noseclip is located. After the ventilator was filled with aerosol, the subject tried to inhale at the mouthpiece, causing an underpressure that initiated the step motor. Thus, aerosol is inhaled at a preselected flow rate, Q_i . After inhalation of the desired aerosol volume, the direction of the ventilator was inverted and the subject exhaled into the ventilator at the preselected flow rate.

During the entire breathing cycle the laser aerosol photometer recorded the respired particle number concentration. Aerosol particle deposition, D , was calculated by integrating the particle number concentration, C , over the inhaled, V_i ,

Table 1. Lung-Function Parameters of the Study Population

Parameter	Patients		Normals	
Number	18		14	
Sex	12 m/6 f		8 m/6 f	
Age (yrs)	60 ± 16		35 ± 6	
VC	3.1 ± 0.91	90 ± 19% pred	5.3 ± 11	113 ± 10% pred
TLC	6.4 ± 1.11	103 ± 14% pred	6.9 ± 11	107 ± 7% pred
ITGV	4.4 ± 1.51	143 ± 42% pred	3.6 ± 0.71	112 ± 19% pred
FEV ₁	1.78 ± 1.11	66 ± 34% pred	4.0 ± 0.91	106 ± 13% pred

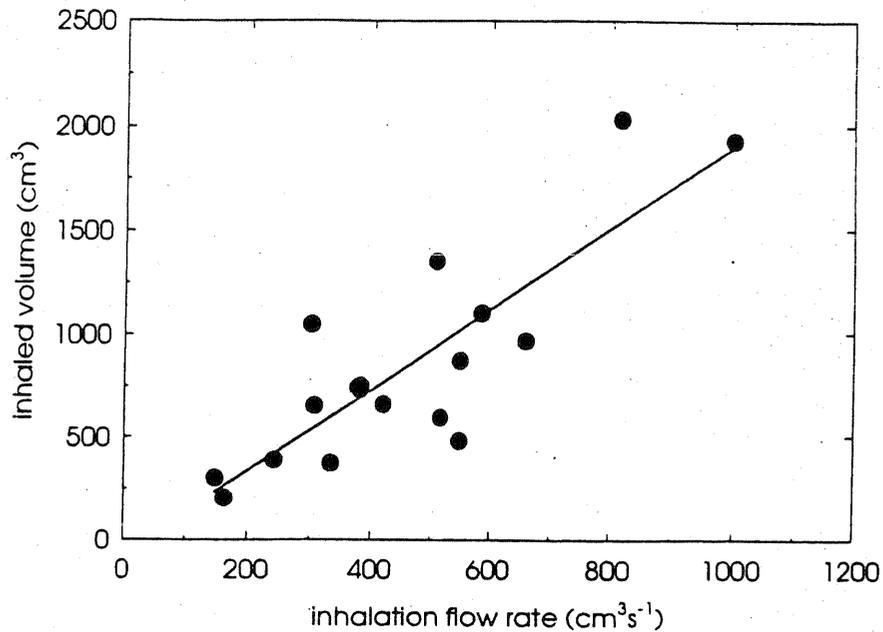


Figure 2. Tidal volume and flow rate measured in 18 patients with lung disease during spontaneous inhalations with a jet nebulizer.

between tidal volume and inhalation flow rate ($r = 0.84$, $P < 0.0001$): Thus, patients inhaling a large volume inhaled with a high flow rate; patients inhaling small volumes inhaled slowly with the result that the time of inhalation was nearly the same in all patients (1.8 ± 0.62 s).

Deposition of 3- μm particles for spontaneous breathing pattern correlated strongly with the flow rate ($r = 0.76$, $P = 0.0002$) (Fig. 3) and the tidal volume ($r = 0.75$, $P = 0.0003$): patients inhaling a large volume at a high flow rate showed high aerosol deposition and vice versa. Average

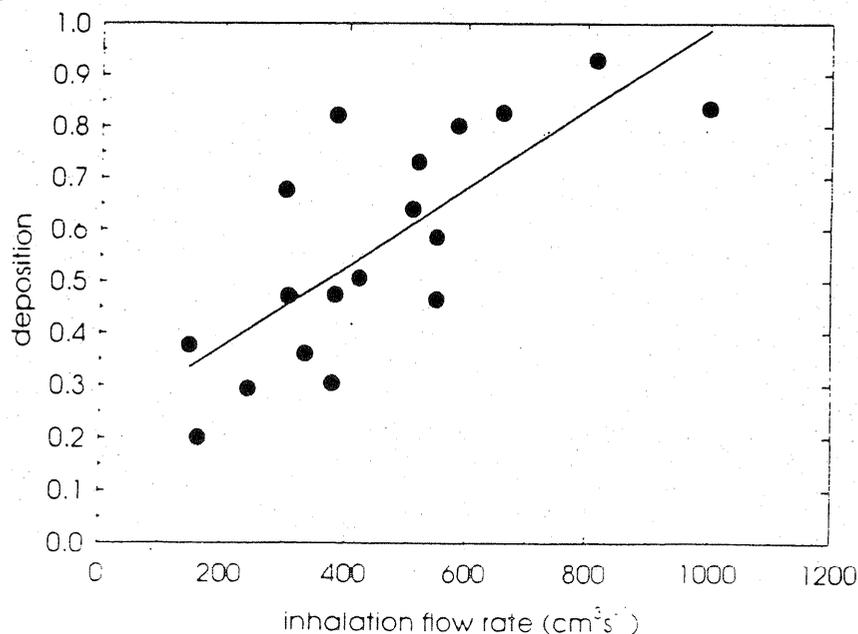


Figure 3. Particle deposition measured with test particles in 18 patients with lung disease as a function of inhalation flow rate.

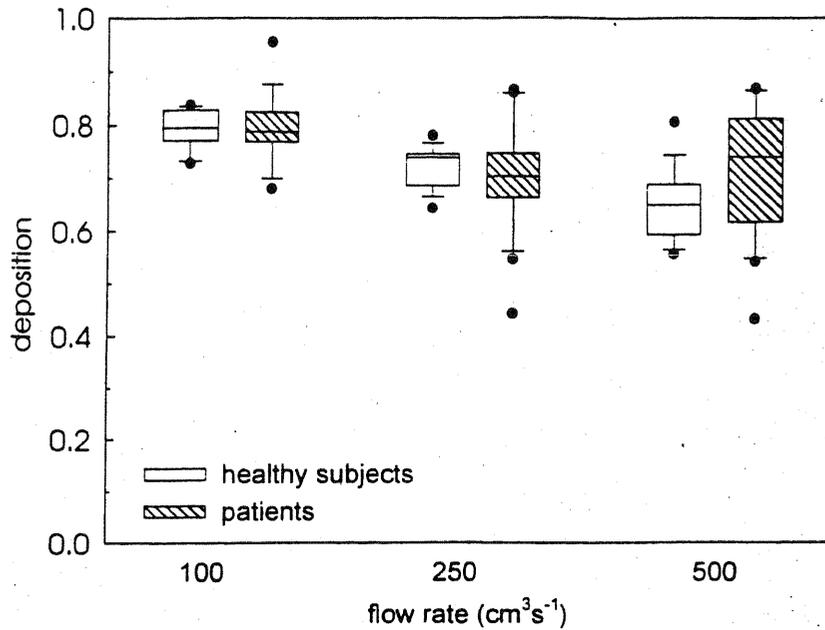


Figure 5. Particle deposition measured in 18 patients with lung disease and in 14 healthy subjects at three different breathing patterns.

For inhalation drug delivery requiring a precise dosage, the large intersubject variability of total deposition measured in this study for a spontaneous inhalation pattern is unacceptable. The data of this study show that the variability of particle deposition within the respiratory system can be considerably reduced if the breathing pattern

is controlled. The variability of deposition for the very slow breathing pattern was about three times smaller than the variability for the spontaneous pattern. This reduction in intersubject variability was air-flow rate dependent (Fig. 5). For slow and very slow flow rates deposition in healthy subjects and in patients is nearly identi-

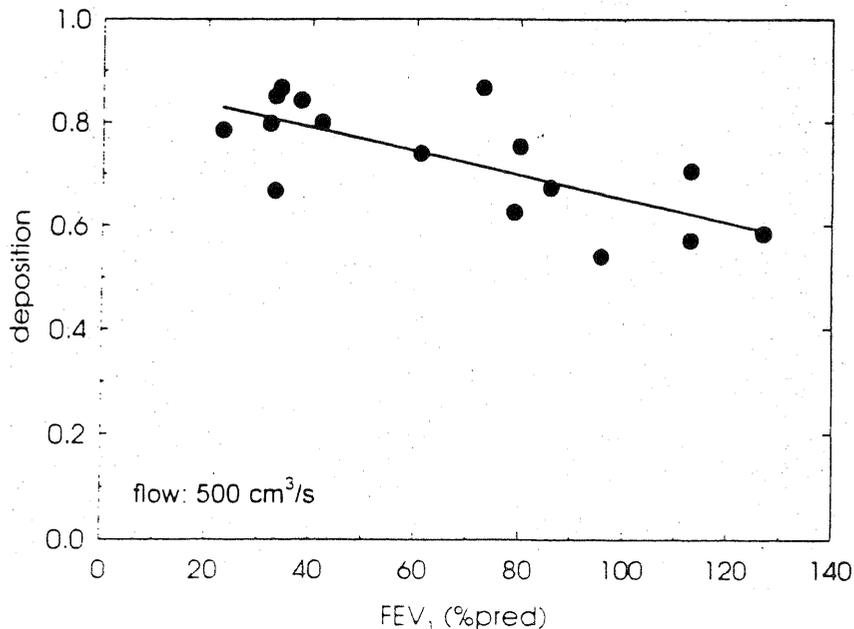


Figure 6. Particle deposition in 18 patients with lung disease at a inhalation flow rate of 500 cm³/s as a function of the forced expiratory volume in 1 s (FEV₁).

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

October 3, 2001

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Notice of Proposed Suspension

FROM: Linda S. Birnbaum, PhD., DABT *Linda S. Birnbaum*
Acting Director, Human Studies Division, MD-58A

TO: Chong Kim, PhD.
Human Studies Division, MD-58D

This memorandum is to advise you that I propose to suspend you from duty and pay status for twenty-one (21) calendar days from your position as Research Physical Scientist, GS-1301-15, Clinical Research Branch, Human Studies Division, National Health and Environmental Effects Research Laboratory (NHEERL), U.S. Environmental Protection Agency, Research Triangle Park, North Carolina. Should a decision be made to sustain this proposed action, the suspension will not begin any earlier than 30 calendar days following your receipt of this notice. This notice of proposed suspension is issued in accordance with Title 5, Code of Federal Regulations, Part 752. The specific reasons for this proposed action are as follows:

Charge: Disregard of a Directive (Federal Regulation)-EPA Order 1000.17 Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research" (first offense)

Background: You have been employed with the U.S. Environmental Protection Agency since August 2, 1990, when you were hired at the top step of the GS-14, as a Research Physical Scientist, with the Human Studies Division, NHEERL. During the past eleven years, you have worked in the Division as a Research Scientist and have progressed to the GS-15 level after having become a National and World expert in the field of aerosol exposures.

As a senior research member and principal investigator (PI) in the Human Studies Division, conducting "hands on" research on human subjects, you are obligated to follow applicable guidelines and protocols that are in place to protect these human subjects and minimize the possibility of liability to the Government. The principal guideline that you

Attachment (6)

are to follow in carrying out these duties is 40 CFR, Part 26, (the Common Rule) titled Protection of Human Subjects, which is attached as Appendix A to EPA Order 1000.17A1, Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research, hereinafter called the Order, dated July 30, 1999. This Order discusses the functions of the Review Official and the Institutional Review Board (IRB). The Review Official is tasked with approving all EPA human studies research before the research starts to include approval of the research protocols to be employed in the study. The IRB monitors the studies once they have started and also approves/disapproves any proposed changes to the protocol methodology. The Order and its provisions are not guidance but are, in fact, the rule of law for conducting human research in the EPA. It is a fact that any changes to the research protocols have to be submitted to the IRB for approval before the change may take place. The responsibility for adhering to these rules falls to the principal investigator who has overall responsibility for the conduct of the research. One important requirement for human studies research is for the PI to prepare and update as necessary the informed consent form which is given to the study participant listing all the potential dangers and side effects resulting from his/her participation in the study. Any pollutant exposures must be listed on the form and there must be a discussion between the PI and the subject regarding the exposure amounts and the likelihood of adverse effects.

You have been involved for some time in a human studies project whereby volunteer subjects are exposed to particulate inhaled in a controlled setting. The particulate used in your most recent study is *diethyl sebacate*. On August 16, 2001, Dr. Philip Bromberg, M.D., University of North Carolina (UNC), Chapel Hill, notified your immediate supervisor, Jim Samet, PhD., in an e-mail of the following concern :

“After my relative euphoria of yesterday concerning possible improvements in the joint PM/dosimetry/modeling research program, I have learned this morning that the amounts of diethyl sebacate particles administered to volunteers in Chong's studies far exceeds what is stated in his approved protocol and consent form.”

Incident to this report, an investigation was conducted regarding the conduct of your research and in particular your adherence to the research protocol established for the diethyl sebacate inhalations. As specified herein, it was determined that you had violated the research protocol in several areas.

Specification 1: Your protocol of record that was filed for this research stated the maximum particle size used in the inhalations would be not more than 50 mcg. The same dose was also stated on the consent form that each volunteer must read and sign. However, it was determined that you were knowingly conducting the experiment using deposited doses which may have exceeded approved levels. In some instances, the doses may have been greater than, or equal to, 1500 mcg, approximately 30 times larger than that listed in the protocol. It is not known at this time whether this increased particle mass has in fact had a detrimental effect on any of the human subjects used in the study. In any event, you used a particle size that was not disclosed to the subject via the

June 2 after inhaling *hexamethonium*, which restricts airways, as part of the study. Besides the attendant adverse publicity that ensued after the untimely death of Ms. Roche, the Government immediately halted all human research at the university following the incident and there is a continuing investigation into the matter.

In determining the proposed penalty for this offense, the Agency's Table of Offenses and Penalties, Appendix A, outlined in EPA Order 3120.1, Conduct and Discipline, was considered. The table lists a penalty range of a written reprimand to a fourteen (14) day suspension for a first offense of "disregard of directive" of which three specifications are listed. This twenty-one (21) day proposed suspension, while exceeding the recommended penalty for a first offense, is prompted by my consideration of applicable aggravating/mitigating factors. You are a long-term senior member of the HSD staff and thus are fully cognizant of the requirements for strict adherence to research protocols. You previously were admonished by memorandum dated December 18, 1997, by your previous supervisor Dr. Robert Devlin, Chief, Clinical Research Branch, regarding your violation of research protocols and were told not to allow any protocol violations to occur again. In that you were previously warned of the consequences of violating research protocols, I am increasing the recommended penalty. This twenty-one (21) day proposed suspension is being proposed to impress upon you the seriousness of your actions and will serve as a warning to you that further instances of these types of failings will neither be tolerated nor condoned.

This proposed suspension, if effected, will promote the efficiency of the Federal Service. You have the right to respond to this proposal orally and/or in writing including any request for consideration of an alternative discipline agreement (Article 39 of Collective Bargaining Agreement) by submitting your response to Dr. Harold Zenick, Associate Director for Health, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Alexander Drive, Research Triangle Park, North Carolina, 27711. Dr. Zenick may be reached at (919) 541-2283.

You will be allowed seven (7) calendar days from your receipt of this notice to submit your written response. Should you desire a meeting in which to present an oral reply to the charges, you must request a personal conference with Dr. Zenick, either in your written reply, or separately, if no written reply is made. Any request for an oral reply must be made within the seven (7) calendar day reply period. Any reply you make will be fully considered in making the final decision.

You have the right to review the material relied on in proposing this action. A copy of the material will be provided to you upon request to the Director, Human Resources Management Division. Subject to making satisfactory scheduling arrangements with your supervisor, you will be allowed up to eight (8) hours of official time to review the material relied upon to support this proposal, and/or to prepare a reply to this notice.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

November 6, 2001

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Notice of Decision to Suspend

FROM: Harold Zenick, Ph.D. 
Associate Director for Health, NHEERL (MD-87)

TO: Chong S. Kim, Ph.D.
Research Physical Scientist (MD-58B)

By memorandum dated and received by you on October 3, 2001, Dr. Linda Birnbaum, Acting Director, Human Studies Division, National Health and Environmental Effects Research Laboratory (NHEERL), U.S. Environmental Protection Agency (EPA), Research Triangle Park, North Carolina, proposed that you be suspended for twenty-one (21) calendar days. The proposal was based on the charge of your "disregard of a directive (Federal regulation) - EPA Order 1000.17, Policy and Procedures on Protection of Human Research Subjects in EPA Conducted or Supported Research".

In that notice, you were informed of your right to reply both orally and in writing to the proposal and the seven (7) calendar day period to do so. On October 4, you sent me an email requesting an extension of the response time. On October 9, I granted your request to extend the response date to October 12, 2001. Accompanied by your representative, Robert L. Davis, you submitted a written statement and made an oral reply to me. I have thoroughly and carefully reviewed the evidence supporting this proposed action as well as your oral and written replies.

First, it is important to provide clarification of two separate activities: one focused on a redirection of your research and the second, addressing disciplinary actions, which is the substance of this memorandum. The former presented in a memorandum from Dr. Birnbaum to you on September 24, 2001, indefinitely banned you from the conduct of human studies with the directive to design a new research program. This assignment which is within the purview of management was done as a safeguard for human subjects protection because of a concern about your "inattention and complacency" in conducting human studies. It is within your prerogative to meet with Dr. Birnbaum to further discuss those actions. On the other hand, the memo from Dr. Birnbaum on October 3, 2001, focused on disciplinary action for these protocol violations and is distinct from the issue of work reassignment. It is within this context that this current letter is now issued.

Attachment (7)

Kim

November 6, 2001

Page 3

what you did was a breach of well-established, valid research standards, even after acknowledging that errors had been made. As worrisome as it is that you violated the protocols and standards of good research, I remain concerned and disappointed that you still do not seem to understand the significance of your actions.

The mitigating factors include the fact that you are a renowned senior research expert and have been truly dedicated in advancing the science in the field of aerosol exposures. As such, the Agency has recognized your accomplishments in the past and again, recently with Scientific and Technology Achievement Awards at Levels II and III. Additionally, other than this particular issue, you have had no past disciplinary actions; are dependable; get along with fellow workers; and show the potential to be able to put this event behind you and move on to other achievements. Therefore, in consideration of all relevant factors, I am mitigating the proposed twenty-one (21) day suspension to a seven (7) calendar day suspension. I believe that this seven day suspension will promote the efficiency of the service and will serve as a deterrent to future violations. Accordingly, you will be suspended for seven (7) calendar days beginning January 2, 2002 and ending January 8, 2002. You are to report for duty at your regularly scheduled time of arrival on January 9, 2002. I have delayed this start date to allow adequate time for you to thoroughly review and provide accurate dose information on each subject so as to expedite any decisions regarding subject follow up. This task should be given priority over any other work you may have scheduled at this time. Following your return to work, you are to adhere to all study protocols, including established procedures for requesting changes. You are advised that future offenses of this nature will not be tolerated and will result in more severe disciplinary action, up to and including your possible removal from EPA employment.

You may contest this action through the negotiated grievance procedure contained in Article 43 of the Master Collective Bargaining Agreement between the United States Environmental Protection Agency and the American Federation of Government Employees.

You are asked to sign and date the acknowledgment copy of this letter. Your signature does not indicate agreement with the contents of this letter but merely indicates that you received it and any attachments thereof.

cc: Dr. Linda Birnbaum (MD-58A)
Dr. James Samet (MD-58D)
Mary S. Day (C639-02)

RECEIPT ACKNOWLEDGED:

Name

Date

2



**OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS**

INTERVIEW OF PHILIP BROMBERG

On May 10, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. PHILIP BROMBERG (919/966-0774), Scientific Director, Center for Environmental Medicine, Asthma and Lung Biology (The Center), and a Faculty Professor of Medicine at the University of North Carolina (UNC) in a conference room on the fifth floor of the EPA Human Studies Building, 104 Mason Farm Road, Chapel Hill, NC. BROMBERG was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

BROMBERG stated at the time of the 2001 over-exposure of di-2-ethylhexyl sebacate (sebacate) to human test subjects related to Dr. CHONG KIM's study, he was the Director, Center for Environmental Medicine and Lung Biology, and a Faculty Professor of Medicine at UNC. BROMBERG stated he also had collateral duties as the Project Officer for Cooperative Agreement between EPA and The Center.

BROMBERG recalled his involvement began when Dr. JAMES BROWN, then a post doctoral student assisting KIM's study, brought to BROMBERG's attention the calculations identifying the overexposure of sebacate to subjects of KIM's study. BROMBERG stated KIM's study identified the number of sebacate particles a subject breathed in and then breathed out. The resulting measurement was the change of what was left numerically in the lungs.

BROMBERG stated he did not know the amount of overexposure the subject's received above their consent, so he could not comment on the allegation of subjects receiving amounts up to 100 times what they consented to receive. BROMBERG knew the subjects received an amount in excess of what they consented to receive. BROMBERG stated he knew Dr. FRED MILLER conducted a review and provided his findings to EPA. BROMBERG stated he considered MILLER an expert and knew him to be meticulous and careful. BROMBERG stated he had 'great confidence in his assessment and judgement'.

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BROMBERG stated after the notification to him from BROWN, he recalled his first notification was to Dr. BOB DEVLIN, the head of the Clinical Research Branch and KIM's supervisor. BROMBERG was also involved after the notification at the invitation of Dr. REITER, the Lab Director, Dr. LINDA BIRNBAUM, and Dr. HAROLD ZENICK and others whom BROMBERG could not recall. BROMBERG stated he viewed it as a chance to offer comments on how serious the problem was as a person outside of EPA. BROMBERG stated there were two concerns: one, a breach of informed consent; and two, the danger the sebacate posed to the subjects. BROMBERG opined KIM's problem resulted from what BROMBERG termed 'protocol creep', which he defined as instead of resubmitting a protocol package incorporating changes for a thorough review by the Institutional Review Board (IRB), the IRB allowed the submission of amendments to the protocol. BROMBERG stated the amendments can happen numerous times to a study and add up to a greater change to the actual study than any individual change allowed. BROMBERG believed that was what happened to KIM's study. BROMBERG did not believe there was any intent by KIM that lead to the over-exposure of sebacate. BROMBERG stated there was no danger to the subjects as a result of the over-exposure and he believed all the subjects were notified of the over-exposure. BROMBERG stated 'no adverse effects ever seemed to have resulted'.

BROMBERG did not believe there was a cover-up of how EPA handled the review of KIM's study and the effects of the over-exposure of sebacate. BROMBERG could not recall a time-line of how quickly EPA acted on the situation, but recalled it seemed like a response was made in an acceptable time. BROMBERG believed EPA officials took the report of the over-exposure of sebacate seriously and made notifications to the highest level. BROMBERG was certain Dr. PETER PREUSS, EPA in Washington, DC was notified of the over-exposure of sebacate.

BROMBERG stated he had no reason to believe BIRNBAUM was involved in not bringing the over-exposure of sebacate information forward. BROMBERG stated he believed BIRNBAUM's attitude was the over-exposure was a 'serious breach' and 'merited serious punishment'. BROMBERG stated he felt the problem was the result of protocol creep that had not resulted in damage to the subject's and did not expect to cause damage. BROMBERG's recollection was BIRNBAUM's response was tougher than what BROMBERG would have given and was in excess to what BROMBERG believed 'fit the crime'.

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INTERVIEW OF ROBERT DEVLIN

On May 10, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. ROBERT DEVLIN (919/966-6255), Chief, Clinical Research Branch (CRB), EPA at the University of North Carolina (UNC) in his office, room number 458, at the EPA Human Studies Building, 104 Mason Farm Road, Chapel Hill, NC. DEVLIN stated he had been the Branch Chief of CRB for about ten years. DEVLIN was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

DEVLIN stated he was on a nine-month detail when Dr. CHONG KIM's study was identified as over-exposing di-2-ethylhexyl sebacate (sebacate) to human test subjects in August 2001. DEVLIN was not involved in the actual handling of the EPA response to the over-exposure or the disciplinary action against KIM. DEVLIN stated Dr. JAMES SAMET was the Acting Chief, CRB at the time. DEVLIN stated he currently is KIM's supervisor and was informed of the situation because he had been KIM's supervisor and was returning after his detail to again be KIM's supervisor again.

DEVLIN stated he was aware of an incident involving KIM about 1996 which involved paperwork and administrative issues by KIM. The 1996 incident did not involve a health issue to any human subjects. DEVLIN stated a letter was put in KIM's file by the Division Director and no action was taken against KIM at that time. Related to the 2001 incident with KIM, DEVLIN stated sebacate was an inert, innocuous substance that KIM used as a model to determine where different size particles of the particulate matter deposited in the lungs. DEVLIN stated KIM's original protocol counted the number of particles because the size of the particles was not large enough to measure their mass. KIM then amended the study to look at larger particles, the mass of which could be measured, but remained focused on the numeric count of the particles, which remained the same, and not the mass. KIM did not account for an increase in mass as the protocol of the study changed to increase the particle size. KIM's metric was the particle count,

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not mass. DEVLIN did not believe there was any intent by KIM to intentionally cause the calculation error. DEVLIN attributed KIM's error to 'sloppy bookkeeping' because he did not take the time to calculate an increase of mass. DEVLIN stated he did not know of any connections KIM had to pharmaceutical companies or other entities which would provide a motive to KIM's error because there was not a commercial application of sebacate.

DEVLIN believed the Institutional Review Board (IRB) would have allowed KIM to use the amount actually given to the subjects, had he submitted the requested protocol changes to the IRB. Had KIM done that, and then received an addendum to the consent by the subjects, the over-exposure would not have been an issue.

DEVLIN stated because of the 2001 incident, KIM could no longer be a principal investigator for human studies with EPA. That restriction was by EPA only and could be revisited by management in the future.

DEVLIN stated Dr. FRED MILLER, who reviewed KIM's calculations, whom DEVLIN considered an expert, identified that the subjects of KIM's study received an amount of the sebacate about 30 - 50 times what they consented to receive. DEVLIN believed the 30 - 50 times estimate was the most accurate estimate of what the subject's received, not 100 times what they consented to as alleged. DEVLIN stated either way, it was not a health issue to subjects for the amount they received. DEVLIN opined there were no health concerns using either amount. DEVLIN stated Dr. RICHARD HERMANN would have information of an FDA study in which human subjects received amounts of sebacate far in excess of even the 100 times figure used by the complainant. DEVLIN stated this was why the subjects were not notified earlier of the exposure to excessive amounts of sebacate greater than they consented to receive. DEVLIN stated if the exposure had affected the health of the subjects, HSD would have notified the subjects sooner. DEVLIN stated the thought process was 'did EPA put the subjects at risk - no' and secondly to 'give the subjects accurate information', which HSD needed KIM's cooperation to do. This caused the delay of notifying the subjects.

DEVLIN stated he did not believe there was a cover-up by EPA in how they responded to the over-exposure of KIM's study. DEVLIN did not believe Dr. LINDA BIRNBAUM was involved in a cover-up or mis-directing EPA's inquiry into KIM's study with the external peer panel review. DEVLIN recalled Dr. JOHN VANDENBERG was the Director of the panel review and BIRNBAUM would have less impact on the review.

DEVLIN did not know the identity of the subject from KIM's 2001 study, who was reported to have recently contacted the EPA because of medical problems, but believed it was coincidental and HERMANN would have details of his identity. DEVLIN stated he believed the subject's medical problem was the result of an ear problem the subject had and the subject's doctor asked if he had been exposed to anything in the past. The subject brought up the EPA study. DEVLIN stated HSD was working with the subject and his doctor to resolve the matter.

DEVLIN opined Dr. TED MARTONEN was the complainant of these allegations. DEVLIN stated he is scheduled to appear June 7 - 9, 2005 in court related to an Equal Employment Opportunity Complaint (EEOC) MARTONEN has against EPA. DEVLIN described the EEOC resulted after MARTONEN perceived his removal from a joint proposal for a study he and KIM conducted as discrimination. MARTONEN was removed from the proposal and replaced with someone else, because the other person had specific experiences that fit better with KIM than

MARTONEN. MARTONEN believed his name was removed because of the letters he sent to the EPA Administrator making complaints. DEVLIN believed BIRNBAUM was the focus of MARTONEN's complaints, and the complaints increased when she became the Division Director and ceased when she was reassigned.

DEVLIN opined MARTONEN believed he was not given enough credit by EPA and not given resources MARTONEN felt he needed for a person of MARTONEN's scientific stature. DEVLIN stated he knew second-hand MARTONEN was considered to be destructive in the work environment. MARTONEN demanded more resources, researchers, money, technicians, a bigger office and a better work-place. MARTONEN believed he was a better scientist than other scientists at EPA. DEVLIN stated Dr. DAN COSTA, a former supervisor of MARTONEN, could provide information BIRNBAUM made requests of resources to support MARTONEN. DEVLIN stated some of those requests were approved by COSTA.

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INTERVIEW OF B. MICHAEL RAY

On May 5, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed B. MICHAEL RAY (919/966-0625), Quality Assurance Officer (QAO), Office of Research and Development (ORD), National Health and Environmental Effects Research Laboratory (NHEERL) at the EPA- OIG office at the EPA Facility at Research Triangle Park (RTP), NC. RAY was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

RAY stated he was a QAO for the Human Studies Division (HSD) for about ten years. RAY currently worked from 104 Mason Farm Road, Chapel Hill, NC. RAY stated the HSD was located on the campus of the University of North Carolina (UNC).

RAY recalled his involvement resulted when Dr. LINDA BIRNBAUM, then Acting Director of HSD, notified RAY of the over-exposure of the di-2-ethylhexyl sebacate (sebacate). RAY stated he interviewed Dr. CHONG KIM, who was conducting the study. RAY reviewed KIM's data and accuracy to understand the over-exposure. RAY stated KIM's research identified how many particles and the location of where the particles settled on the lungs. RAY stated the IRB approved the study. RAY stated the study protocol limited the ability to measure particle mass, and KIM's research measured particle count, not mass. RAY stated he found no evidence and had no belief KIM intentionally overexposed the human test subjects. RAY opined the over-exposure was the result of sloppy research by KIM. RAY stated the quality review he conducted on KIM's work was okay. The research data was accurate. RAY stated KIM amended the breathing maneuver the subject's used during the experiment, which caused the subjects to breath in more particles than before.

RAY could not remember who told him, but recalled hearing KIM believed the over-exposure was an insignificant amount, which may be why KIM did not request approval from EPA. RAY stated KIM should have received formal approval from EPA if there was a significant change to protocol. KIM received the approval from the IRB, but not EPA.

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RAY stated JIM BROWN, a UNC graduate student at the time, brought the over-exposure error to KIM's attention. RAY believed JACKY ROSATI was also a PHD candidate at the time who was involved in the KIM study.

RAY referred reporting agent to Dr. FRED MILLER's September 11, 2001 report to BIRNBAUM which reported the dosage amount range of sebacate given to the subjects. RAY stated Dr. SEAL was responsible for contacting the subjects of KIM's study.

RAY did not see any evidence of a cover-up of the inquiry into KIM's over-exposure of sebacate given to the subjects. RAY opined the over-exposure could not harm the test subjects health.

RAY stated corrective action resulted from the review of the over-exposure in KIM's study. RAY stated studies now measure the units of what the safety level for a particular substance is.

RAY was asked if he could identify a motivation of someone who brought the information to the OSC. RAY stated he did not know who would make a complaint, but the motivation could be political. RAY again stated he thought the issue was resolved three years ago and that there was not a cover-up.

RAY concluded that at the time of KIM's over-exposure, he was not required to look at the mass value. Because KIM did not look at the mass value, he had no way of knowing the study was exceeding the safety limits of the amounts consented to by the subjects. RAY stated KIM could have done the calculations to determine the mass change. RAY stated those measures are now included with tests of human subjects.

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INTERVIEW OF JAMES M. SAMET

On May 5, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed JAMES M. SAMET (919/966-0665), Principal Investigator, Clinical Research Branch (CRB), Human Studies Division (HSD), National Health and Environmental Effects Research Laboratory (NHEERL) at a conference room located on the fourth floor at the EPA Human Studies Facility, 104 Mason Farm Road, Chapel Hill, NC. SAMET was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

SAMET stated he was the Acting Chief of the CRB filling in for Dr. BOB DEVLIN, who was detailed to another position. Having been the Acting Chief for about a week during August 2001, he was informed by an e-mail from Dr. PHIL BROMBERG, University of North Carolina (UNC) of the dosage calculation problem related to the study by Dr. CHONG KIM. SAMET recalled JIM BROWN, a UNC graduate student, informed BROMBERG of the calculation error. SAMET stated he notified his supervisor, Dr. LINDA BIRNBAUM, Acting Division Director, that same day within hours of receiving the e-mail from BROMBERG.

SAMET recalled the main concern was to determine if the over-exposure was a health risk to the subjects. SAMET recalled the subsequent discussions over the next few days determined the over-exposure was an extremely unlikely health concern or safety concern to the human test subjects. SAMET opined the Institutional Review Board (IRB) would have approved the dosage amount if presented as a protocol change, because the di-2-ethylhexyl sebacate (sebacate) was an inert matter. SAMET stated the concern was because the subjects were exposed to the sebacate at an amount greater than they gave consent for exposure.

SAMET stated KIM kept amending the protocol of his study. SAMET stated KIM did not take into consideration the increased mass of a particle as the diameter size of a particle increased. SAMET stated he would provide the calculations to the reporting agent of how mass grew

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exponentially as size increased. The formula to determine mass is:

$$\text{Mass} = \text{Pi}/6 * d(\text{cube}) * \text{rho}$$

SAMET stated the increase of mass was not accounted for in the subject's consent form.

SAMET opined the errors by KIM occurred because of sloppiness and inattention to detail on KIM's part. SAMET stated KIM's fractional deposition study considered the size of the particle. Mass was a secondary consideration. SAMET stated the letters sent to the subjects may have varied in what was reported (the 30 - 50 times exposure to the consent to receive) because the amount given to each subject varied as part of the test.

SAMET stated he did not believe there was a cover-up to the study. He opined there was no evidence of symptoms or negative health effects of the subjects as a result of the study of over-exposure of sebacate.

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INTERVIEW OF FRED MILLER

On May 9, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. FRED MILLER (919/467-3194), formerly and during 2001 the Acting Vice President of Research at the Chemical Industry Institute of Toxicology (CIIT), at MILLER's residence located at 911 Queensferry Road, Cary, NC. MILLER stated CIIT is now CIIT Centers for Health Research. CIIT is an organization that received grants to conduct different studies of health and environmental factors. MILLER stated he retired from the position about six months ago when the position was eliminated. MILLER stated he was an EPA employee until the late 1980's, when he began working for CIIT. MILLER was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

MILLER stated he did not receive any compensation for CIIT's sole source procurement. MILLER recalled CIIT received \$10,000 to have MILLER review the number's of Dr. CHONG KIM's particulate matter study of testing how di-2-ethylhexyl sebacate (sebacate) settled in and around the lungs when it was determined in August 2001, human test subjects were given an amount of sebacate in excess of what they consented to receive. MILLER provided his experience as over 20 years in research programs related to breathing and inhaling particulate matter. MILLER's field of study was dosimetry models, which was the study of the amount of matter in the body and how it deposited itself in the body and transferred to other areas of the body.

MILLER stated he became involved in reviewing the calculations from KIM's study during August 2001. MILLER produced a report based on his review, dated September 11, 2001, and addressed to Dr. LINDA BIRNBAUM. That report addressed the completed study of KIM and the human test subjects who were Chronic Obstructive Pulmonary Disease (COPD) subjects. MILLER stated the subjects received no effects (negative) from the excessive dosages of sebacate because there was a minimal toxicity to sebacate. MILLER stated there was more of a

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concern of subjects who were asthmatics because the problem with asthmatics was not that the particulate was toxic, but that it was present, even though it was innocuous. MILLER stated his review did not find any effects from the asthmatic group either. MILLER stated he was not aware of any attempt by EPA or BIRNBAUM to cover-up KIM's errors which lead to the excessive dosage of sebacate given to human test subjects of KIM's study. MILLER stated if his nine recommendations contained on page 10 of the September 11, 2001 document were not addressed by EPA, then that would be the only way he would be concerned of a possible cover-up by EPA.

MILLER also produced a more detailed report with numeric values of the amount of sebacate actually induced by the human test subjects on March 15, 2002. That report was addressed to Dr. SAMET. MILLER stated the March 15, 2002 report of the Assessment of Potential Maximum Dose in Adeposit Subjects assumed a worst case scenario because the protocols KIM used for the study were bad. As KIM's study changed, the later protocols did not resemble the original protocols of the study. MILLER stated because he could not establish a base line because of KIM's poor protocols, MILLER used a worse case assumption of KIM's studies, and his calculations indicated a 50 - 60 times exposure of sebacate to the subject's to what they actually consented to receive. MILLER stated any exposure problem identified by the subjects would have occurred immediately. MILLER stated if a person came forward today with health risks they attributed to KIM's study, it would never hold up. MILLER stated his involvement with the KIM matter ended with the March 15, 2002 report.

MILLER did not believe KIM had an agenda or any connection to a group, such as a pharmaceutical company, which would cause him to intentionally violate the protocols and provide an excessive amount of the sebacate to the subjects. Instead, MILLER opined KIM was naive when it came to administrative issues of his studies, and was careless. MILLER had known KIM professionally since the 1980's. MILLER stated KIM's study went through the Institutional Review Board (IRB) with broad protocols. KIM made minor changes to the study and the IRB approved the changes, but did not identify the dosage-error resulting from the study changes. MILLER stated the IRB should have identified protocol changes would have affected the dosages the subjects were exposed to receive. MILLER stated what KIM did was change the methodology but did not recognize the need to report calculations of the new methodology.

To put the amount of sebacate the human subject's received in perspective, even at 60 times what they consented to, MILLER referenced a study involving 200 gram hamsters that were given 8000 units of the sebacate with no adverse health effects. MILLER stated that was more than twice the amount in whole units given to any test subject. As a contrast, MILLER used the above example with a human subject weighing about 180 pounds and receiving 3000 units of sebacate.

MILLER stated he would be "suspicious" if TED MARTONEN was making the allegations to OSC. MILLER stated MARTONEN could not interact well with others. MILLER opined other people had been burned by MARTONEN's ego. The only other person MILLER believed would possibly make the allegations to OSC would be JIM BROWN, a researcher on KIM's study, if BROWN believed in his consciousness, that things were missed during the previous investigation of this matter.

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INTERVIEW OF ELSTON SEAL

On May 9, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. ELSTON SEAL (919/942-7965), EPA retired. SEAL was assigned to the Human Studies Division (HSD) of the National Health and Environmental Effects Research Laboratory (NHEERL) as the Human Subjects Research and Review Official, also known as the Medical Ethics official, during 2001. The interview was conducted at the Office of Inspector General office location at Research Triangle Park (RTP), NC. SEAL was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

SEAL stated he recalled a study in August 2001 involving Dr. CHONG KIM in which human subjects received di-2-ethylhexyl sebacate (sebacate) during a particulate matter test. SEAL opined he had more involvement in KIM's study because he was the medical ethics official at the time of KIM's study. SEAL stated he would become involved when there were violations of human research protocols. SEAL stated he would prepare the protocols to respond to situations, answer questions, and work to resolve issues related to questions of medical testing of human subjects.

SEAL recalled JACKY ROSATI, a graduate student who was working on KIM's study, identified calculations which lead to the excess dosage of sebacate given to KIM's subjects. SEAL recalled KIM submitted an amendment to the protocol of his study, but failed to recalculate the inhaled particles as the study protocol changed.

SEAL stated sebacate had a large margin of safety and did not believe any subjects were given an amount 100 times what they consented to. To put it in context, SEAL stated had anyone received an amount 100 times what they consented to, even though it sounded like a lot, it was not. SEAL stated he recalled Dr. FRED MILLER's report as accurate with a 50 - 60 times the consented dosage of sebacate given to the subjects. SEAL recalled MILLER's figures were based on a

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worst case scenario of recalculating the dosage of sebacate given to the subjects by KIM. SEAL stated the worst case scenario was used because a good baseline of figures could not be used because of how KIM conducted his study. SEAL stated he would consider the numbers of 50 - 60 times provided by MILLER of what the subjects consented to receive as accurate, in contrast to the numbers provided by the complainant in the allegation that the subjects received an amount of sebacate up to 100 times what they consented to receive.

SEAL recalled an external review panel recommended about 20 items for EPA to address in it's procedures with human testing. SEAL recalled EPA adopted virtually all the recommendations. SEAL stated he reported to Dr. HAROLD ZENICK the progress of the panels recommendation.

At this point during the interview, SEAL asked if the allegations resulted from a complaint from TED MARTONEN. The source of the complaint was not revealed by the reporting agent. SEAL advised he believed MARTONEN was a known schizophrenic and had 'issues' with Dr. LINDA BIRNBAUM.

SEAL stated he put together the original time line of the report given by EPA to the external review panel during their 2002 review. SEAL also stated he was the person who made the decision to halt KIM's study. SEAL stated he contacted the Recruitment Office to stop recruiting for testing. SEAL also stated he instructed them not to schedule any others for the study, and to cancel any standing appointments for KIM's study. SEAL stated he also contacted the Nursing Section, which was a redundant notification, to ensure the study was halted. SEAL recalled he notified ZENICK at the time as well.

SEAL recalled there was a delay notifying the subjects of the over-exposure of sebacate pending MILLER's review and findings. SEAL stated he also made notifications to the Office of General Counsel (OGC) and Public Affairs (PA), with additional notifications to EPA PA and the Congressional Affairs Office in Washington, DC. SEAL recalled coordination between the Institutional Review Board (IRB), PA, OGC, the Division Office, ZENICK, and again to the same entities of any changes to the notifications to the subjects, slowed the notification process to the subjects. SEAL stated the belief at the time was they could take their time because the over-exposure to the subjects was not harmful or a health risk to the subjects.

SEAL stated he did not believe there was a cover-up by EPA of KIM's study giving subjects an overexposure of sebacate. SEAL stated he never felt anyone at EPA covered up the incident. SEAL stated he had the full support of ZENICK, Dr. LINDA BIRNBAUM, and Dr. JOHN VANDENBERG. SEAL stated IRB chair DAN NELSON stated EPA handled the over-exposure episode of the KIM study 'extremely well'. SEAL also stated Dr. ERNEST PRENTICE, the chairman of the external review panel, said EPA had handled the KIM situation in a responsible way.

When asked if a person receiving the over-exposure nearly four years ago would have a health problem currently, SEAL said no. He stated sebacate was commonly used in the cosmetics and food industry. SEAL recalled about eight people contacted EPA regarding the notification letters. SEAL opined the purpose of their contacts was reassurance from EPA.

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INTERVIEW OF DAN NELSON

On May 10, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. DAN NELSON (919/966-1344), Director, Institutional Review Board (IRB), University of North Carolina (UNC) at a conference room in Building # 52, UNC, Mason Farm Road, Chapel Hill, NC. NELSON was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

NELSON stated he was the Director of the IRB that oversaw Dr. CHONG KIM's study prior to the halting the study in 2001 due to the over-exposure of di-2-ethylhexyl sebacate (sebacate) identified as given to human test subjects in August 2001. As reference, NELSON stated there were eight IRB's, four of which were bio-medical, like the one that oversaw KIM's study. NELSON was a member of the four bio-medical IRB's. The IRB's normally met weekly to ensure all administrative taskings were in order. The other four IRB's were Public Health, Nursing, Dental, and Academic. NELSON stated his position was permanent and he was an employee of UNC. He added Dr. STEVE BERNARD's position as Chair of the IRB's was an appointed position by the Dean at UNC.

NELSON stated it was common to make changes to the studies before the IRB's, normally to adjust, increase or decrease what was tested, or other modifications to a researcher's study. NELSON stated as part of the IRB review process, risk to human subjects was considered. NELSON stated the studies were not supposed to move forward without IRB approval. He stated the IRB relied upon the paperwork and information from the researcher or principal investigator to make decisions. NELSON stated if a researcher failed to provide information, the IRB may not be aware of problems. THE IRB relied on the trust of the researcher following the protocols and knowing the rules. The IRB would review the proposed methodology and make modifications on paper, before approving the study, or changes to the study.

NELSON stated researchers were supposed to have their modifications to studies approved by

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the IRB. NELSON stated most researchers did that, however, some did not because they incorrectly believed the changes were within their domain.

NELSON stated EPA investigated KIM's study to support the IRB. NELSON recalled he received initial notification of the over-exposure of sebacate to human subjects from Dr. SEAL.

NELSON recalled EPA notified the IRB immediately and began an investigation when EPA identified KIM's study was over-exposing subjects to sebacate in amounts greater than they consented to receive. NELSON stated initially he believed over-exposure was about two times what the subject's consented to. He advised he believed the final result was the amount Dr. FRED MILLER identified as 30 - 50 times over-exposure to the subjects as what they consented to receive. NELSON stated the IRB's issue was not necessarily the amount of the over-exposure of sebacate, but the fact that an over-exposure of what the subjects consented to receive actually occurred without the subjects approval. NELSON stated that was the bigger problem because sebacate was considered an innocuous substance and not a health risk to human subjects. NELSON had no basis to believe the subjects received amounts greater than 30 - 50 times what they consented to receive, as based on Dr. MILLER's review. NELSON stated the IRB did not approve KIM giving an increased amount of sebacate to the subjects without a modification to the protocol, but in review, likely would have approved such a modification, as the amount given to the subject's was an innocuous amount and not a threat to human health. If the approval was given, the subject's would have been given an addendum to the original consent form. If new subjects were used, a new consent form with the appropriate amount of exposure of sebacate would have been given to the subjects. NELSON believed there was nothing to base a blame of intent on KIM to create the over-exposure dosage error.

NELSON did not believe there was a cover-up by EPA into the investigation. NELSON stated on a scale of one to ten, with ten being completely open and one a cover-up, he'd rate EPA's handling of the situation a ten. NELSON described that once EPA detected the over-exposure of sebacate to what subjects consented to receive, EPA was responsive and initiated a review to identify the cause. NELSON believed EPA realized there were systemic issues and took planning mechanisms to respond to the problems identified. NELSON opined EPA did more than the IRB would have done to resolve the issue, specifically related to the level of concern by EPA and the insight to which they reviewed the situation. NELSON stated it was 'hard to see a cover-up because of bringing in an outside panel'. NELSON reiterated EPA went 'above and beyond' what the IRB would have done to resolve the issue.

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF JACKY ROSATI

On May 11, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. JACKY ROSATI, Environmental Scientist, National Homeland Security Research Center, at her office, Building E, Room # E311C, at the EPA Facility at Research Triangle Park (RTP), NC. ROSATI was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

ROSATI stated she was a pre-doctoral candidate and EPA grantee student in August 2001 at the University of North Carolina (UNC) under Dr. CHONG KIM. ROSATI stated she was not assigned to KIM's study of particulate matter deposits of di-2ethylhexyl sebacate (sebacate). ROSATI stated her employment with EPA began September 2002.

ROSATI stated Dr. JAMES BROWN (now her spouse), was working on KIM's sebacate study during August 2001. ROSATI stated BROWN replaced SHU-CHEIH HU on the study, because HU moved to the Chicago, IL area. ROSATI recalled she commented to BROWN on the dilution of sebacate as an aerosol. ROSATI stated BROWN thought her findings were different from what he had seen in KIM's sebacate study. ROSATI stated they used the instrumentation from her lab to conduct tests in BROWN's lab. ROSATI stated she was familiar with the protocol of KIM's sebacate study because the protocol was the same in the study she was conducting for KIM. ROSATI stated she finished the study under Dr. WILLIAM BENNETT because KIM was removed from her study as a result of the over-exposure. ROSATI stated her study was also shut down as a result of the over-exposure incident.

ROSATI recalled from her recollection of the protocol, the concentration of sebacate the human subjects received in KIM's study may have been about 100 times what the subjects actually consented to receive. To put the amount in perspective, ROSATI stated sebacate had been used in human and animal studies since the 1960's. ROSATI stated she put together a report that was used by Dr. WILLIAM BENNETT, which had information of amounts of sebacate used in tests with human subjects at exposures greater than the actual amounts KIM's subjects received,

Investigation Conducted on: May 11, 2005	Conducted at: Research Triangle Park, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 12, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>

without any effect. ROSATI stated there was no toxic data of sebacate. ROSATI did not believe there was a health problem due to the over-exposure of sebacate the subjects received. ROSATI believed the more important issue was the integrity of the consent or contract the human subjects agreed to with EPA.

ROSATI did not believe there was a cover-up by EPA of the KIM study. ROSATI stated she believed EPA made an immediate response once informed of the over-exposure.

ROSATI stated Dr. TED MARTONEN and KIM were on her dissertation committee. ROSATI opined KIM and MARTONEN had 'bad blood' between them. ROSATI cited KIM would produce data for MARTONEN to model, and instead gave the data to CLEMENT KLEINSTREUER at North Carolina State University. ROSATI believed there was competition in the National Health and Environmental Effects Research Laboratory to be the only EPA person to publish research, which may have been a cause of KIM giving the data to KLEINSTREUER. ROSATI stated this occurred prior to 2001, but was unsure exactly when.

ROSATI believed MARTONEN knew of BROWN's involvement with KIM's study because of 'scuttlebutt' in EPA. ROSATI recalled MARTONEN may have called BROWN to tell him what BROWN did was the right thing to do. ROSATI stated she probably did talk to MARTONEN at some time about the over-exposure in KIM's study.

ROSATI stated she did not believe there was a cover-up of the incident by EPA. ROSATI stated KIM was removed from studies as a result. Because of KIM's removal, her studies finished under BENNETT. ROSATI stated she did not know of any questions regarding the amount of over-exposure to sebacate to KIM's study prior to August 2001.

ROSATI described MARTONEN as neurotic and denied she had talked to MARTONEN prior to August 2001 of the over-exposure despite MARTONEN's claim he spoke to her prior to August 2001 about the over-exposure of sebacate to human test subjects.

ROSATI believed HU had tested the sebacate at one time and that it came with-in the protocol range. ROSATI believed HU never followed up. ROSATI stated her belief was based on HU's personality as she knew him. ROSATI described HU as not a 'go-getter' to get literature to understand the study better. ROSATI did not believe anyone had intent to over-expose subjects and nobody knew of an exposure until BROWN's calculations were reported during August 2001.

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF JOHN P. GILMAN

On May 17, 2005, Special Agent (SA) LEONARD O. NEWMARK, Desk Officer, Financial Fraud Directorate, telephonically interviewed JOHN P. GILMAN, former EPA Assistant Administrator, Office of Research and Development at (865) 241-4659. SA NEWMARK identified himself and informed GILMAN that the purpose of this interview was to identify his involvement in review activities associated with human subject research conducted by Dr. CHONG KIM at EPA's National Health & Environmental Effects Research (NHEERL) Laboratory, Research Triangle Park, North Carolina. GILMAN provided the following information:

GILMAN stated that he left EPA on November 20, 2004, however in early 2003 the sebacate dosing errors associated with KIM's experiment were brought to his attention by LARRY REITER. GILMAN did not recall any specifics of this situation, but recalls reviewing emails associated with this issue. GILMAN stated that while the sebacate exposure deviated from the experimental protocols, it did not pose any harm to the human subjects.

GILMAN stated that LINDA BIRNBAUM did not downplay the significance of the sebacate exposure and in fact, took steps to contact the Department of Health and Human Services to benchmark what to do. GILMAN also stated that BIRNBAUM had little or no role with respect to the outside review committee set up to study this situation. BIRNBAUM did not set the agenda, PETER PREUSS did.

GILMAN stated that while someone may think that EPA was not being diligent in addressing this issue, he disagreed. GILMAN said that the human subject testing program had been put on hold for six to eight months to study the exposure situation.

Investigation Conducted on: 05/17/05	Conducted at: Washington, DC
Conducted by: SA Leonard O. Newmark	OI File No: 2005-0002
Date Prepared: 05/23/05	Prepared by: LON

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EPA Form 2720-15 (Computer)

INTERVIEW OF JOHN P. GILMAN

GILMAN stated that he is currently the director of the Oakridge Center for Advanced Study located in Oakridge, TN. GILMAN's email is "Paul.Gilman@ORAU.org."

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF CHONG S. KIM

On May 19, 2005, SA DAVID L. COTNER, Special Investigations Unit, and SA LEONARD NEWMARK, Financial Fraud Directorate, interviewed Dr. CHONG S. KIM, (919/966-5049), Physical Research Scientist, Human Studies Division (HSD), EPA, Chapel Hill, NC, at a second floor conference room, 104 Mason Farm Road, Chapel Hill, NC. KIM was shown proper identification. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC) by Dr. TED MARTONEN, alleging KIM exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of KIM.

KIM stated he had been an EPA employee since 1990. KIM stated his supervisor was Dr. BOB DEVLIN. KIM worked at Mt. Sinai Medical Center in Miami, FL prior to working for EPA. At this time, KIM was shown EPA Form 2720-18, Warning and Assurance to a Federal Employee requested to provide Information on a Voluntary Basis. KIM volunteered he had no intent to give subjects dosages of sebacate above the level they consented to receive. KIM wanted to cease the interview to think about signing the form because paragraph two stated anything KIM said could be used against him in any future criminal proceeding or agency disciplinary proceeding, or both. KIM was concerned because he believed he had been disciplined previously as a result of this incident. (AGENT's NOTE: Investigation determined KIM had received previous disciplinary action as a result of his role as the Principal Investigator of his study of di-2-ethylhexyl sebacate [sebacate]).

After about a one hour break, KIM decided to continue the interview and signed EPA Form 2720-18 (Attachment 1). KIM stated his sebacate study was a long-term study which lasted about ten years. KIM stated when the over-exposure of sebacate was discovered, the study ceased and was never re-started by HSD. KIM stated he could no longer conduct human studies and received a suspension as a result of the over-exposure. KIM described the study as a inhalation study designed to study the ratio of sebacate aerosol breathed in and out by a subject.

Investigation Conducted on: May 19, 2005	Conducted at: Chapel Hill, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 19, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>

KIM stated the study measured the sebacate that was inhaled and exhaled and looked at the ratio related to particle size and the deposition of sebacate in the lung. KIM stated the estimated dosage was recorded on the consent form the subjects signed.

KIM stated over time the protocol of his study changed. As an example, KIM cited the subjects originally took ten breaths. As the study progressed, the subjects subsequently took fifteen, then twenty breaths. KIM stated his study methodology did not consider dosage an issue, but rather the ratio of sebacate particulate matter. KIM stated that was because sebacate, which was the only substance used for inhalation studies, was an inert, innocuous substance without health risks to the subjects. KIM stated as he was developing different protocols for his study, the question of the accuracy of the dosage of sebacate the subjects received was identified by post-doctoral student JAMES BROWN. KIM stated the study needed more accuracy to re-evaluate the dosage level of sebacate given subjects. KIM stated the dosage level was not measured because of the size of the particulate matter, rather math formulas were used to identify the dosage level. KIM described the study as measuring the electrical signal, or voltage, of what went in the lungs and where it went, then calculating the ratio. KIM stated mass was not measured with the original protocols because the particle size was too small. KIM stated as the particle size increased, the dosage level changed.

KIM stated mass had never been a concern of his study because low dosages of sebacate, about fifty micrograms, were given in a short exposure window, which did not cause any adverse health effects. KIM stated about fifty people participated in the study, including his son, JEFF, who participated in the study while a University of North Carolina student about six years ago. KIM stated he did not believe there were any complaints or negative health effects as a result of the over-exposure of sebacate by anyone who participated in the study. KIM stated Dr. ELSTON SEAL, now retired, but the EPA Medical Ethics Officer at the time, was responsible for contacting the subjects of KIM's study.

KIM stated in hindsight, as a result of his experience with the sebacate study, KIM would be more concerned about mass of any future studies. KIM stated it was a mistake that mass was not part of the protocol. KIM cited the oversight because sebacate was considered inert. KIM stated he would calculate the dosage of sebacate correctly in the future, examining all aspects. KIM stated there was absolutely no intent to over-expose the subjects of his study. KIM stated he did not have any interest with pharmaceutical companies and did not own any financial interest in pharmaceutical companies.

KIM stated no one, including Dr. TED MARTONEN, had seen his log books of data (including subject data) related to his sebacate study. KIM stated although he collaborated on a couple articles with MARTONEN, there was no way MARTONEN had access to data to calculate the dosage of sebacate given to subjects.

KIM stated he did collaborate with MARTONEN and did provide experimental data to MARTONEN to conduct math modeling to validate the model for the both research papers. KIM stated the collaboration with MARTONEN was forced by the two different EPA divisions he and MARTONEN were assigned to. KIM stated the time-frame was the mid to late 1990's for both papers. KIM stated providing experimental data was different from providing the log books of data. KIM stated he did give MARTONEN the experimental data. KIM stated MARTONEN did not have enough data, specifically base-line data, to make calculations to determine the dosage the subjects received. KIM stated the base-line was on the subject consent form, and

MARTONEN did not have that information, and because of that, it was impossible to make accurate and true calculations. KIM stated mathematicians could make assumptions and theorized that may have been what MARTONEN did. KIM reiterated there was no way MARTONEN would know as fact the amount of sebacate given to subjects during KIM's study. KIM stated MARTONEN did not have access to subjects of KIM's study. KIM had no idea if MARTONEN had tried to contact KIM's subjects through any other means. KIM wondered if any study participants knew MARTONEN.

KIM did not have a reason MARTONEN implicated KIM with MARTONEN's allegations. KIM opined MARTONEN may have been using him. KIM stated the last time he spoke to MARTONEN was over six months ago. KIM stated he had not spoken to MARTONEN about KIM's study outside of the collaboration using experimental data in the mid to late 1990's, or any other studies.

KIM believed the subjects were exposed to sebacate at a rate of forty to fifty times what they consented to receive. KIM stated the allegation the subjects received sebacate at one hundred times what they consented to receive was too high. KIM stated there was not an EPA cover-up, and cited his suspension and ban from conducting human studies by Dr. LINDA BIRNBAUM as evidence she did not cover-up anything or mis-direct the Human Subject Review Panel. KIM stated BIRNBAUM was the Acting Division Director, HSD, at that time.

KIM stated sebacate was the only substance tested in his sebacate study. KIM stated there was no control for his study, because he was not looking at effect, but dispersal of the sebacate. KIM stated he was sure MARTONEN knew EPA took steps to address the over-exposure of sebacate given during KIM's study. KIM stated he did not have any idea why MARTONEN would make the allegations to OSC.

KIM declined to make a statement at this time.

Attachment

1. EPA Form 2720-18, Warning and Assurance to a Federal Employee requested to provide Information on a Voluntary Basis, dated May 19, 2005

**OFFICE OF INSPECTOR GENERAL
U.S. ENVIRONMENTAL PROTECTION AGENCY**

**WARNING AND ASSURANCE TO A FEDERAL EMPLOYEE
REQUESTED TO PROVIDE INFORMATION ON A VOLUNTARY BASIS**

You are being contacted to solicit your cooperation in an inquiry regarding allegations of misconduct or improper performance of official duties. In accordance with the Privacy Act of 1974, you are advised that the authority to conduct this interview is contained in the Inspector General Act of 1978, as amended.

This matter under investigation could also constitute a violation of law which could result in criminal prosecution of responsible individuals.

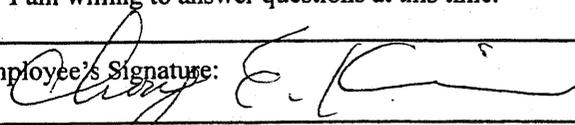
This inquiry pertains to False statements related to over-exposure
of D-2-ethylhexyl sebacate to human subjects.
(State the general nature of the inquiry)

Before we ask you any questions or you make any statement, you must understand the following warnings and assurances.

1. You have the right to remain silent and refuse to answer any questions at any time.
2. Anything you say can be used as evidence against you in any future criminal proceeding or agency disciplinary proceeding, or both.
3. If you refuse to answer the questions posed to you on the ground that the answers may tend to incriminate you, you cannot be discharged solely for remaining silent. However, your silence can be considered in an administrative proceeding for its evidentiary value that is warranted by the facts sounding your case.

WAIVER

I understand the warnings and assurances stated above. I waive my rights freely and voluntarily, without threat or intimidation, and without any promise of reward or immunity. I am willing to answer questions at this time.

Date: 5/19/05	Time: 4:20 PM	Employee's Signature: 
Witnessed by: Edward Turchak		Title: Special Agent
Witnessed by: 		Title: SA
Place: Chapel Hill, NC		
Case Number: 05-0002		

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF REBECCA CALDERONE

On May 11, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. REBECCA CALDERONE (919/966-0617), Director, Human Studies Division (HSD), EPA at the University of North Carolina (UNC) in her office, room number 152, at the EPA Human Studies Building, 104 Mason Farm Road, Chapel Hill, NC. CALDERONE was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

CALDERONE stated at the time of the identification of the over-exposure of di-2-ethylhexyl sebacate (sebacate) from Dr. CHONG KIM's study involving human subjects, she was the Branch Chief, Epidemiology and Biomarker Branch (EBB). CALDERONE stated she was not involved with the external review panel and did not have any input putting together the HSD PM notebook (Attachment 1). CALDERONE stated the HSD PM was a collection of EPA documents contained in a binder related to EPA's review of the over-exposure of sebacate given to KIM's subjects. CALDERONE stated the HSD PM was also provided to the Human Subject Review Panel (HSRP) to assist their external review of KIM's study. CALDERONE did attend meetings where KIM's over-exposure was discussed, but was not involved with any decisions because EBB was not involved with KIM's study.

CALDERONE recalled KIM's over-exposure study was well known within EPA and did not believe EPA covered up anything related to KIM's study. CALDERONE believed Dr. LINDA BIRNBAUM could not have influenced the external peer review panel because Dr. JOHN VANDENBERG was the main point of contact for the external peer review panel. CALDERONE recalled Dr. ROGER CORTESI of EPA in Washington, DC was also a point of contact to the HSRP. CALDERONE stated with her position as Director of HSD, she had been involved with corrective action memos related to KIM's over-exposure study. CALDERONE stated HSD reviewed their policy yearly and planned to bring a similar external peer review panel to UNC to review HSD's policies this year.

Investigation Conducted on: May 11, 2005	Conducted at: Chapel Hill, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 11, 2005	Prepared by: SA David L. Cotner <i>guc</i>

CALDERONE stated Dr. TED MARTONEN had made a similar allegation about a year ago. CALDERONE stated she was asked by then Assistant Administrator PAUL GILMAN to provide information through his staff person, MICHAEL MOORE so GILMAN could respond to MARTONEN's allegation. CALDERONE believed that incident about a year ago was the second allegation made by MARTONEN, as she recalled a conversation with either MOORE or BIRNBAUM which referenced a prior allegation by MARTONEN.

CALDERONE stated she would also obtain copies of Dr. FRED MILLER's September 11, 2001 and March 15, 2002 letter; a copy of the most recent memorandum reviewing HSD policies; a copy of the adverse action memorandum given to KIM; and a copy of an FDA study which documented human subjects had received amounts of sebacate well in excess of the amount of the over-exposure KIM's subjects received, without adverse health risks. CALDERONE stated she would notify the reporting agent once she had retrieved all the copies.

Attachment:

1. HSD PM Notebook

Enclosures:

- a. Incident Summary
- b. Protocol(s)
- c. Consent Forms
- d. Amendments(s)
- e. Approvals
- f. Education/Certificate
- g. Adverse Event Report
- h. Letters to Subjects
- i. SOPS
- j. Data
- k. QA

HUMAN STUDIES DIVISION

PM

Problems Identified and Solutions Implemented in Response to PM Protocol Violation

Problem	Immediate Action	Long Term Action
<p>In August 2001, EPA was informed of a protocol violation; the mass of inert particles given to subjects in a dosimetry study exceeded what was specified in the protocol. (PM Time line 8-16-01)</p>	<p>Immediate notification of the IRB. (PM Time line 8-16-01)</p> <p>Suspension of all studies conducted by the responsible PI. (PM Time line 8-17-01)</p> <p>Immediate notification of NHEERL Management. (PM Time line 8-17-01)</p> <p>Examination of all studies conducted by the PI for other potential protocol violations. (PM Time line 8-20-01)</p> <p>PI provided estimate of maximum dose that could have been delivered to subjects; pulmonary physicians and experts in dosimetry were consulted, who determined it was very unlikely this dose caused harm to the subjects. (PM Time line 8-20-01) (PM Time line 9-17-01)</p> <p>Based on this consultation, EPA elected to postpone notification of subjects until accurate estimates of dose delivered to each subject could be calculated (IRB concurred). (PM Time line 9-10-01)</p>	<p>New HSD Policy: On-site engineering support contractor will be responsible for preparation and delivery of pollutants for all inhalation studies. (Vol.1:Tab 3 Proposed HSD Policies)</p> <p>Disciplinary action taken against the investigator (settlement in late December). (PM Time line 12-31-01)</p>

<p>Not all consent forms were signed by the investigator. (PM Time line 8-20-01) (Vol.2:Tab 1 Incident Summary)</p>	<p>Meeting with PIs to discuss the protocol violations and reinforce the need for careful attention to detail. (PM Time line 8-20-01)</p> <p>Thorough review of consent forms from all HSD studies (no other violations discovered). (PM Time line 8-21-01)</p>	<p>New HSD Policy: Medical Station now checks consent forms daily to ensure proper signatures. (Vol.1:Tab 3 Proposed HSD Policies)</p> <p>Investigator training expanded. (Vol.1:Tab 6 Training)</p>
<p>Personnel added to the protocol without IRB notification and approval. (Vol.2:Tab 1 Incident Summary)</p>	<p>Study audit workgroup formed to conduct a broad vulnerability analysis of all HSD human studies. (PM Time line 8-22-01)</p>	<p>If new personnel are added to a study, an amendment to that effect must be submitted to the IRB; new EPA policy provides better EPA management oversight of all amendments. (Vol.1:Tab 3 Proposed HSD Policies)</p> <p>Investigator training expanded. (Vol.1:Tab 6 Training)</p>
<p>Inattention to detail by the investigator. (PM Time line 8-22-01)</p>	<p>All hands meeting to discuss current environment concerning all human studies and to reinforce vigilance in adhering to guidelines for performing human studies. (PM Time line 8-30-01)</p>	<p>Additional training implemented, including mentoring of new investigators and refresher training for current investigators. (Vol.1:Tab 6 Training)</p>
<p>Protocol was amended numerous times over several years without sufficient management oversight. (Vol.2:Tab 1 Incident Summary)</p>		<p>New HSD Policy: All amendments will be reviewed by the Branch Chief, Division Director and the NHEERL Human Subjects Review Official before they are submitted to the IRB. (Vol.1:Tab 3 Proposed HSD Policies)</p> <p>New HSD Policy: No protocol can be active longer than 5 years. (Vol.1:Tab 3 Proposed HSD Policies)</p>

Calculation of particle dose received by each subject was needed to prepare letters to subjects; calculations are complex.
(PM Time line 8-20-01)

Calculations required the assistance of the PI, and could not be undertaken until after disciplinary settlement in December.
(PM Time line 10-29-01, 12-31-01, and 1-30-02))

P.I. calculated dose delivered to each subject.
(Vol.2:Tab 10 Data)
Because of the complex nature of the calculations, an outside dosimetry expert was engaged to validate the approach taken by the PI.

(PM Time line 9-17-01)
(Vol.2:Tab 10 Data)

Letters sent to subjects.
(PM Time line 6-06-02)

Incident Time Line: PM Protocol

8-16-01 Dr. Philip Bromberg (Director, University of North Carolina Center for Environmental Medicine and Lung Biology - UNC CEMLB) alerted Dr. Jim Samet (Acting Chief, Clinical Research Branch - CRB), Dr Dave Peden (UNC Collaborator), and Dr. Bob Devlin (CRB Branch Chief on detail) that it appeared from calculations done by a UNC CEMLB collaborator that the dose of di-2-ethylhexyl sebacate particles listed in an HSD PM protocol with an HSD PI substantially exceeded what was stated in his approved protocol and consent form.

Dr. Elston Seal (NHEERL's Human Research Subject Official) was informed that the research principal investigator (PI) apparently violated the terms of his research protocol. The UNC Institutional Review Board (IRB) was notified by Dr. Seal that the violation had occurred.

8-17-01 Dr. Seal spoke with Dr. Linda Birnbaum (Acting HSD Director) and agreed that Dr. Hal Zenick (Associate Director for Health) should be notified. Dr. Seal called the HSD Subject Recruitment Office and the HSD Medical Station to inform them the PI's studies were suspended.

Dr. Birnbaum notified Dr. Zenick of the breach in the research study protocol.

Dr. Zenick requested a bulleted list of "what is known" by the end of the day and it was provided to him.

8-20-01 The PI provided dose information indicating that the maximum human dose of di-2-ethylhexyl sebacate was 1.5 mg, which is about 30 times more than what the PI thought the dose to humans in his study was.

Dr. Seal met with Dr. Birnbaum, Dr. Samet and Mr. Mike Ray (HSD QA Officer). It was agreed that the major issue was non-compliance with the terms of the protocol. Subject safety was a lesser issue given the nontoxic nature of the sebacate, but we were relieved that no one appeared to have been injured. Dr. Seal was asked to look into the following things:

1. Check to see if all investigators, techs, and post docs were listed on protocols (they were not).
2. Check protocols to see if the maximum dose of aerosol was listed and if the PI (or his assistants) consented subjects with this in the consent form (he did). However, in reviewing the consent forms, a large number were incomplete with respect to signature of the PI.
3. Make copies of the correspondence from the 1997 incident with the same

PI and gave them to Dr. Birnbaum.

Mr. Ray sent an e-mail to Dr. Birnbaum recommending that calculating the particle dose for each subject be considered because lung deposition varies with particle diameter and individual subject variables.

HSD management meeting with CRB Principal Investigators. Discussed human research "white paper" (now the NHEERL draft Policy Guidelines for the Conduct of Human Research), protocol deviations, closing loopholes, and holding a meeting to discuss protocols in development.

8-21-01 Ms. Maryann Bassett (HSD nurse) notified Dr. Seal that the nurses had reviewed all current study charts for signature compliance on consent forms and found no problems in other investigators' studies.

Dr. Seal met with NHEERL Senior Management (Dr. Lawrence Reiter, Director of NHEERL, Dr. Zenick, Dr. Birnbaum, Dr. Devlin, Dr. Samet), and Dr. Bromberg to discuss issue.

Dr. Seal met with Dr. Birnbaum, Dr. Devlin, and Dr. Samet to discuss course of disciplinary action concerning the PI, pending discussion with Human Resources Management Division (HRMD).

The PI wrote to Dr. Birnbaum stating that at least half of the unsigned consent forms belonged to subjects who were cancelled and never participated in the study.

8-22-01 Dr. Seal received a copy of an e-mail from the PI claiming that incomplete consent forms might be an oversight in some cases and that other forms were for subjects not actually studied. Dr. Seal replied that folders with incomplete consent had subject data in them and that Dr. Seal stood by the previous numbers of improperly executed consent forms.

Dr. Birnbaum updated Dr. Zenick on the dosimetry study problems in a summary as follows:

1. Documented evidence and responses from the PI regarding protocol deviations in three areas:
 - a. Maximum deposited dose exceeded what was stated in the IRB approved protocol.
 - b. At least one investigator worked with subjects and had not been added to the protocol.
 - c. ~20 % of consent forms were not signed.

2. The IRB had been sent formal interim notification of the protocol violation and that the study had been stopped pending an investigation. HSD stated that we strongly believed that no subject was harmed. HSD also let the IRB know that a more detailed report would be sent once our investigation was completed.
3. An all hands meeting was scheduled for August 30 to discuss the current environment concerning all human studies, and the need for all to be exquisitely attentive to protocol requirements.
4. Two groups had been convened which produced preliminary recommendations:
 - a. A study audit group (for exposures conducted by the investigator rather than TRC - Operations, Modification, and Maintenance contractor for the Human Studies Facility).
 - b. A subject safety working group.
5. Alerted Mr. Mark Sullivan and Ms. Ramona Litowsky, both in HRMD, to the problem.

8-23-01

Dr. Seal sent a list of protocol violations to Dr. Birnbaum.

Dr. Birnbaum added 'investigators interacting with subjects without being added to the protocol' to Dr. Seal's list.

In a message to Dr. Birnbaum, Dr. Zenick requested an approximate time table for the parallel activities that were being carried out.

In response to Dr. Zenick's request, Dr. Birnbaum sent an e-mail outlining the steps that were being taken. She told Dr. Zenick that HSD was moving on all fronts. The IRB had already been notified, the protocol had been suspended and the PI had been asked for an accounting of the problems. A preliminary QA of the PI's efforts had also been conducted. A review of other protocols indicated that the problems were confined to his studies.

HSD asked Dr. Fred Miller of the Chemical Industry Institute of Toxicology (CIIT) to do a risk estimate of the maximum dose deposited in the lungs, i.e., a worst case scenario. The estimate was expected after Labor Day.

HSD drafted a letter to the IRB informing them of what the problem was, our steps to remedy the situation, and future steps. The letter would be sent in the

next week, but would require additional follow up when Dr. Miller's risk analysis was received.

HSD was in the process of developing procedures to strengthen management oversight of all human studies. A new policy had been instituted that a nurse would be an integral member of all projects. A group had been convened to develop this new approach. Enhanced QA procedures were undergoing development.

An all hands meeting was planned for the following week to lay out new procedures and policies and answer questions.

The letter concluded with a message that we were taking this incident very seriously and that progress was being made in many areas.

8-30-01 Human Studies Division - All Hands Meeting

8-31-01 Dr. Zenick summarized the actions taken by Dr. Birnbaum (here printed in its entirety):

"Per our conversation, I understand the following to be the actions to date and time lines since we met.

1. Following the informal phone call to Mr. Dan Nelson, Chair of the IRB, HSD sent a brief memo to him this week noting that violations of an approved protocol had occurred and that HSD was collecting information to provide the IRB with a complete picture including any risks the subjects may have experienced although the initial sense is that subjects safety was not compromised. Did your brief note address that the follow up letter would also 1.) Outline the actions taken and seek IRB comment and additional suggestions and 2.) Provide a risk statement so as to obtain IRB guidance on the need to contact the subjects?
2. The information gathering phase has been concluded including a QA audit and review of all subjects consent forms. The PI has provided comment on the three violations.
3. The week of 9/3, a risk estimate is to be provided by Dr. Miller, CIIT.
4. Actions to implement safeguards have been, are being, implemented including a meeting with staff on Thursday to reiterate stringent requirements for protocol review and approval, including modifications.

5. In parallel, you have had discussions with HRMD.
6. If the risk estimate is in hand this coming week, you anticipate a memo back to the IRB fully detailing the situation, noted corrective actions that have been set in place in HSD and seeking their advice on those actions as well as guidance on subjects follow up.
7. Because of the substantial amount of work that will be needed to identify the subset of subjects exposed to the higher mass, you have delayed that search until getting IRB advice.

Please correct or modify my impressions.

Thanks"

Dr. Birnbaum wrote a letter to Dr. Zenick, with a copy to Mr. Sullivan, summarizing the issues and discussing options for disciplinary action. She recapped the issues which are the PI's contribution to NHEERL and his international recognition in the area of particle deposition. She went on to point out his inattention to detail, and a previous protocol problem in 1997..

Dr. Birnbaum then outlined the current problems:

1. Exceeding the maximum stated dose of particles by a factor of 20-30 fold.
2. Lack of signed consent forms.
3. Allowing a collaborator who had not been added to the consent form to participate in the study.

She also pointed out that there were some anecdotal reports of violations from the medical station which were not as easy to pinpoint. Dr. Birnbaum blamed, in part, a failure of management and process controls for the problems. A series of investigator education meetings and "alertness training" was recommended. There followed a section on Management Actions and disciplinary action.

9-6-01 Dr. Birnbaum wrote to Dr. Zenick with her recommendations regarding protocol violations.

Dr. Seal sent a letter to the Committee on the Protection of the Rights of Human Subjects informing them of what was known to date and what we had done to prevent further incidents like this from happening in HSD.

9-10-01 Dr. Birnbaum provided a draft letter, including a table of corrective actions, to the IRB for Dr. Zenick's review. She also mentioned that Dr. Miller promised to mail his report the next day. It included recommendations on auditing procedures and

a path to follow to get an accurate determination, rather than worst case estimates of deposited dose.

- 9-12-01 Ms. Jeanne Galbo (Dr. Miller's secretary) wrote to Dr. Birnbaum at Dr. Miller's request providing the files of the work Dr. Miller had done on the data. Ms. Galbo stated that Dr. Miller had told Dr. Birnbaum that there were difficulties with the PI's files and that he hoped that we were able to resolve them. She also said that Dr. Miller would follow the electronic message with hard copies.
- 9-17-01 Mr. Ray wrote to Dr. Birnbaum with recommendations for review of the PI's studies. Mr. Ray stated that he had read Dr. Miller's report of September 11, 2001 and had briefly reviewed the PI's data. Mr. Ray believed that a peer scientist should independently review the original exposure data, and estimate the actual particle mass for each subject. He went on to say that the PI's original data consists of electronic files composed of traces, similar to chromatograms, that relate subject breathing patterns to voltage responses of a light scattering measuring instrument. The files reside on a workstation in the PI's lab. Mr. Ray further stated that it was beyond his expertise as a QA specialist and analytical chemist to independently retrieve and interpret the data. Mr. Ray's recommendation was for a scientist experienced in particle lung deposition research to ensure that all original data was retrieved from the workstation, that the original traces be properly interpreted concerning the number and duration of breaths taken, that the number and size of the particles related to each subject's breath be determined, and that the individual exposures for each subject be appropriately combined to arrive at the total particle mass exposure for each subject.
- 9-19-01 Dr. Birnbaum wrote to Dr. Seal, Dr. Samet, and Dr. Devlin with a message that she had written to Ms. Patricia Jackson (NHEERL Deputy Director for Management, Acting) asking how the Division could facilitate getting a review done - maybe under an existing peer review contract or an existing health and safety contract.
- 9-20-01 Ms. Jackson wrote to Dr. Birnbaum stating that she had spoken with Mr. Marshall Gray (EPA Safety Office). Mr. Gray said that their contract might fit her needs but he was not sure.
- 9-21-01 Mr. Ray wrote a memo describing a contract to have data analyzed and sent it to Dr. Birnbaum. He summarized the situation in two parts, first, Background, in which the protocol was described. Subjects were exposed to di(2-ethylhexyl) sebacate (DEHS) under varying conditions of particle size, breaths per minute, airflow rate, particle concentration, and aerosol dispersity (mono vs. polydisperse). Two types of exposure regimens were being studied; one involving

bolus delivery of the aerosol and the other, non-bolus delivery. The protocol indicated that five different groups would be studied: Young normal subjects (age=18-40 yrs.), older normals (age>60 yrs.), cigarette smokers (age -18-40 yrs.), asthmatics (age=18-40 yrs.), and COPD patients (age>40 yrs.). The protocol noted that the polydisperse aerosol regimen was restricted to 20 young normal subjects, otherwise, all age groups would be studied in the various combinations of breathing frequency, particle size, and flow rates. Gender differences were being examined indirectly, in that male and female subjects had been recruited. The protocol states that the total lung dose of DEHS particles per subject is expected to be <50 micrograms. It is the accuracy of this last statement which is being questioned.

The second part of the memo deals with the Required Tasks for this contact:

- “1. Obtain and review all research data from the protocol’s principal investigator concerning subject exposures, including downloading electronic files that relate to subject breathing patterns to voltage responses.
2. Determine the number and duration of breaths taken by each subject and the number and size of particles related to each subject’s breath.
3. Determine the total mass exposure for each subject taking into account the time between visits and the subject’s grouping within the five groups described in the first part of the memo.
4. Prepare and submit a report to EPA that describes the procedures used to perform tasks 1-3, that tabulates by subject the data obtained in tasks 2 and 3, and that includes copies of all research data in task 1, including an explanation for any data not used in preparing the report.”

Dr. Seal provided a copy of the first letter sent to the IRB to Dr. Samet, Dr. Birnbaum, Dr. Zenick, and Dr. Reiter.

Ms. Jackson forwarded Mr. Ray’s contract requirements to Mr. Gray for his consideration.

9-26-01

Dr. Seal received a response to his letter of 9-6-01, from the IRB Chair acknowledging the HSD’s handling of the incident and for looking beyond it into subject safety matters in all HSD clinical research.

10-9-01

Mr. Gray sent a message to Ms. Jackson with a copy to Dr. Birnbaum stating that the request for contract support was way beyond the capabilities of the National

Technical Assistance Contract.

10-15-01 Dr. Birnbaum wrote a memo to Dr. Zenick about determining the dose in the studies. In this memo, she stated that determining the actual mass deposited would not be a trivial effort, and would require a great deal of technical expertise. After much thought and discussion, Dr. Birnbaum believed that the best way to get this information was to have the PI do it because we needed his cooperation to do the calculations. His review of his data could be followed by random audits on his analysis. She thought this would be the most effective and timely way to do this. She continued with a statement about investigating mechanisms with Ms. Jackson to accomplish these random audits, and asked if she should proceed in this direction.

10-22-01 Dr. Birnbaum wrote to Dr. Samet and Dr. Seal asking whether Dr. Jim Brown was a post doc or a technician, since the PI questioned whether is was necessary for him to be listed on the protocol.

Dr. Zenick wrote to Dr. Birnbaum, and copied Mr. Sullivan, that the PI believed the third problem (failure to include investigators on the protocol) to be erroneous. The PI claimed that IRB policy only required that they be informed when a PI/co-investigator was added to the protocol. The PI stated that Dr. Brown was only serving as a technician and there was no need to report his involvement.

Dr. Zenick asked if there was HSD policy which was more specific on this point. He also asked for a clearer statement, perhaps from Dr. Brown, as to which aspects he was engaged in.

Dr. Birnbaum wrote to Dr. Zenick that we would check with Dr. Brown as to his role. Dr. Birnbaum expressed the idea that he was more than a technician. She also stated that she would look into Division policy. We had a statement from the IRB that states that all who work on a protocol need approval. Dr. Birnbaum would send a copy to Dr. Zenick.

10-23-01 Dr. Samet replied that Dr. Brown could be looked at either way since he was currently a post doc but would soon be or was recently appointed a research associate.

10-26-01 In response to the PI's claim that Dr. Brown should not be listed as an investigator, Dr. Birnbaum sent Dr. Zenick an e-mail from Dr. Seal dated April 9, 2001 to all of NHEERL, that puts in writing the requirement for all working on a protocol to be listed and have approval. Many other investigators in HSD had technicians listed on protocols, but the PI listed only himself and coinvestigators. However, the IRB has told HSD that they want all listed.

Dr. Brown stated that both he and the PI ran subjects, sometimes together, sometimes when the PI was not in the room. In those cases, Dr. Brown did the coaching on the breathing patterns by himself. This appeared to be more than just a technician running the equipment.

- 10-28-01 Dr. Zenick wrote to Dr. Birnbaum asking her to respond to the PI's letter in which each of his points was addressed in a constructive manner. Dr. Zenick mentioned that he would be issuing his disciplinary memo early that week, and he would like Dr. Birnbaum's memo to be transmitted on the same date or before his. Dr. Birnbaum wrote to Dr. Zenick stating that she had her response ready.
- 10-29-01 Dr. Birnbaum wrote a memo to Dr. Zenick explaining that an outside evaluation of the dose was needed to determine as accurately as possible how much inhaled material each subject received. The PI's assistance would be needed in this process. Dr. Birnbaum and Ms. Jackson had discussed alternative mechanisms for conduct of the analysis.
- 10-30-01 Dr. Samet sent an e-mail informing Dr. Birnbaum the PI said it would take one day per subject to calculate the dose of particles that each subject received.
- 10-31-01 Dr. Birnbaum wrote to PI that his first priority was to determine the dose deposited in his subjects. He was instructed not to work on anything else until the dose calculations were done. One month after the dose calculations were completed, he was expected to have his draft future research proposals ready.
- 11-02-01 Dr. Samet wrote to the PI that as they had discussed two days before, it was imperative that the PI focus all of his time on calculating the actual dose delivered to the subjects in the ADEPOSIT study. Dr. Samet went on to say that no other task has priority over this. Furthermore, Dr. Samet asked in order to get an idea of the time line of this process, that management ask the PI to first provide an estimate of the number of subjects who are known to have received more than the 50 microgram dose stated in the consent form. Dr. Samet also mentioned Dr. Miller offered to provide a software package that he believed would be very helpful in performing the calculations.
- 11-6-01 Dr. Zenick sent the PI an e-mail memorandum containing his decision regarding disciplinary action. It was followed by a formal memorandum that the PI was asked to sign only as an acknowledgment of receipt and then return it to Dr. Zenick's office.
- 11-13-01 Dr. Samet wrote to Dr. Birnbaum that he had a discussion with the PI about the estimation of dose of particles delivered to the subjects in the study. The PI related to Dr. Samet that there were substantial problems with the regeneration of

the data, most troubling was the clunky data acquisition software that was used, creating an unavoidably time and labor intensive process no matter who did it. The PI also said that the software that Dr. Miller offered would not be helpful in this specific task but that it might be useful after the data was reconstructed.

Dr. Samet suggested that the PI consider evaluating the five or 10 subjects who received the highest dose on visual inspection of the data tracings. The PI said that this could be done. Then this data could be used to calculate the mean plus or minus a standard error of the estimated upper-bound limit of the dose that each subject would have received. The dose of all of the subjects would fall under that value. This worst case could be used to inform subjects that they received no more than $Y \pm Z$.

Dr. Samet went on to say that he had discussed this idea with Dr. Miller who thought it might work. This sample would be small enough to allow the "audit" to involve the entire data set used to generate the upper-bound estimate and could be done collaboratively with the PI. Dr. Samet thought this was the way to go.

- 11-14-01 Dr. Samet wrote to the PI he thought there was a plan approved by Dr. Birnbaum and that we needed to get back to Dr. Miller to get one of his people involved in the process.
- 11-19-01 Dr. Samet wrote to the PI that the performance of the delivered dose calculations as required by the IRB was the PI's highest priority to determine the number of subjects affected. Dr. Samet let the PI know that Dr. Birnbaum also emphasized that this was the highest priority. Further, Dr. Samet asked when he could expect the results of the calculations.
- 11-21-01 Dr. Birnbaum requested from Dr. Samet an update about the fate of the PI's student and post doc to update Dr. Zenick.
- 11-26-01 Dr. Samet informed Dr. Birnbaum that Dr. Hao Hua Tu, a CEMLB appointed post doc, was now working on an in vitro modeling dosimetry study that represented a significant change from his previous activities. Ms. Jackie Rosati, an Environmental Science and Engineering (ESE) doctoral student, was working with Dr. William Bennett, who was now her official dissertation advisor.
- 12-3-01 Dr. Birnbaum wrote to Dr. Samet that she had sent the PI e-mails stating that the calculation of dose was his number one priority (e-mail to the PI and cc'ed to Dr. Samet on 10-31).
- 12-21-01 Dr. Samet wrote to the PI emphasizing that Dr. Birnbaum had asked him to contact the PI about the analysis of subject exposures. Dr. Samet emphasized that

the first step would be the calculation of the number of subjects affected by the incident.

12-31-01 The disciplinary action concerning the PI was settled.

1-9-02 Dr. Birnbaum wrote the PI an e-mail stating that it had been several months since he was directed as the highest priority to work on the dose calculations for the subjects in his study and that she would like to have this information as soon as possible.

The PI wrote to Dr. Birnbaum that he had been working to get reasonable estimates of the dose for his subjects, because there was no way to get absolutely accurate doses. The PI went on to say that going into the raw analogue data was not practical and an assistant would not be of much help in this complicated task. He had finished the calculations for thirty subjects and had twenty more to do. He hoped to be able to present the results to her. If Dr. Birnbaum accepted his reasoning and results, the PI hoped to be able to wrap things up by the end of that week.

1-30-02 The PI sent two files, one of the dose table and another of a draft letter to subjects, to Dr. Birnbaum.

In a memo to Dr. Zenick, Dr. Birnbaum stated that she tried to contact Dr. Miller to get information for a Professional Services Contract (PSC). The message also included the calculations from the PI with an explanation of how he performed the calculations.

2-6-02 Dr. Birnbaum queried Dr. Samet about the PSC issue. She wanted it in place quickly.

Dr. Samet said that he had spoken with Dr. Miller that afternoon and they considered approaches that could be taken (i.e., a QA on the PI's calculations, an independent estimation of dose or a combination). Dr. Samet e-mailed the PI's description of his calculations to Dr. Miller and he would reply with recommendations. Dr. Samet explained the urgency and the scope. Dr. Miller was expected to get back to Dr. Samet very soon. Ms. Jo Ann Fuller (HSD Program Analyst) was ready to put together a PSC as soon as Dr. Samet could write the Statement Of Work, which he would do after hearing from Dr. Miller.

2-7-01 Dr. Seal wrote to Dr. Reiter, Dr. Birnbaum, Ms. Jackson, and Dr. Zenick telling them that he had prepared a Power Point presentation of the protocol violation and the Division's response and asked if they wanted to have the presentation e-mailed to them or have it presented to them. He asked for dates if they wanted it

presented to them.

Dr. Zenick responded to Dr. Seal's offer of a presentation with a request to see the Power Point briefing in advance and have a full briefing with a time line of events.

2-08-02 Dr. Seal prepared a draft of a letter to be sent to the participants in the PI's studies. The letter was sent to Dr. Zenick, Dr. Birnbaum, Dr. Devlin and Dr. Samet. He asked for feedback from those to whom it was sent.

2-11-02 Dr. Miller sent files that he thought would be of assistance to Dr. Samet and Dr. Birnbaum. Dr. Miller also wanted to make Dr. Samet and Dr. Birnbaum aware that he thought EPA would need to go beyond the calculations for the 5 micron particles. His thinking was driven by two points: The first is that the concentration may have been higher for the 3 micron particles (and the 1 micron particles) such that when the regional deposition fractions for the various particle sizes are taken into account, the deposited dose for one of them (most likely the 3 micron particles) may actually have been higher than the 5 micron dose. Second, the time between exposure to the various particle sizes for the same dose is not specified. If the same subject was exposed 3 days in a row to the 3 different particle sizes, then there is a much greater delivered dose and potential risk than if the exposures occurred several weeks apart. Dr. Miller concludes that for what EPA may have to convey to the study subjects concerning potential risks, this would make a big difference.

Dr. Birnbaum replied to a message from Dr. Samet asking that if the PI's estimates for the 5 micron doses were OK could we then decide if we need to look at the 3 micron exposures as well. Dr. Birnbaum said to do things stepwise.

Dr. Birnbaum requested that the PI do the calculations for deposited dose when 3 micron particles were used. She also asked if any of the subjects were exposed on consecutive days.

2-12-02 The PI reported to Dr. Birnbaum that there were 13 subjects who came two consecutive days. It will take some time to do the calculations for these subjects, therefore a completion date for this task is difficult to determine. The PI speculates that Dr. Miller is trying to estimate cumulative dose. The PI suggests to get data from a few subjects for this purpose, but not to spend a lot of time on this.

Dr. Birnbaum wrote to the PI concurring with his suggestion to focus on a few subjects to see if the 3 micron information makes a big difference. She asked the PI to do this as his highest priority.

A PSC was awarded to Dr. Miller at CIIT for an audit of the PI's calculations.

2-25-02 As previously planned, Dr. Birnbaum returned to her position in the Experimental Toxicology Division and Dr. John Vandenberg became Acting Director of HSD.

3-4-02 HSD worked on a revision of the briefing documents which had been prepared by Dr. Seal.

3-18-02 Dr. Samet sent an e-mail that CIIT had sent a copy of their audit report (in actuality, an independent calculation of the data). Two subject's data were assessed. In one case the PI's calculations underestimated the deposited dose (2.8 mg vs. 1.8 mg) and in the second case the calculations agreed very well (2.5 mg vs. 2.4 mg.). The authors of the report felt that the discrepancy was likely because of differences in assumptions caused by uncertainties regarding the default values in the calculations. There was also some debate over the need to calculate the 3 micron particle data. Dr. Miller believes that it is absolutely essential while the PI believes that it is readily calculated using the 5 micron data.

Dr. Birnbaum wrote that the decision about calculations for the 3 micron data should be made quickly in order to notify the subjects.

3-19-02 Dr. Samet wrote to Dr. Zenick he believed the purpose of the outside analysis was not to check the PI's arithmetic, but to verify that the approach was fair, reasonable, and scientifically defensible. Dr. Samet believed that the key issue is how much difference is acceptable. Dr. Bahman Asgharian at CIIT told Dr. Samet that the agreement is in the acceptable range. Dr. Samet goes on to say that Dr. Miller is at Society of Toxicology (SOT) meeting and will not be available until next week. Dr. Samet planned to get Dr. Miller's perspective when he returns the following week. Dr. Samet agrees that management should insist that the PI calculate the 3 micron data because it will be lower than the 5 um data, but certainly higher than the 50 microgram that the subjects were told they would receive.

Dr. Zenick sent a memo to Dr. Samet, Dr. Birnbaum and Dr. Vandenberg (new Acting Director of HSD) stating that he appreciated the efforts to date but that the issue was one of scientific credibility. He speculated that perhaps Dr. John Creason (HSD Biostatistician) or another statistician could define what a credible size population for analysis would be. He asked Dr. Vandenberg, since Dr. Birnbaum was on travel, to follow up with Ms. Jackson as to the current effort and the need to revisit a suitable vehicle to complete a credible analysis and provide a report to the IRB and with their guidance get a letter to the subjects.

Dr. Zenick wrote that he had two concerns about the task CIIT performed. They

were that data from two subjects seemed inadequate, especially to explain to ORD Senior Management. He believed that several other records should be examined. Dr. Zenick also believed that because of the need to inform subjects of doses greater than they agreed to, the data for subjects exposed to 3 micron particles should also be examined.

Dr. Birnbaum responded to Dr. Samet's earlier memo with the thought that his responses were reasonable and that we do need the calculations of the 3 micron particle doses, at least for a subset. She goes on to say that the doses modeled by CIIT seemed to be in good agreement with the PI's calculations. If it is necessary for CIIT to model more subjects, another PSC would be necessary. She asked if Dr. Zenick wanted Dr. Samet to initiate another PSC.

3-20-02

Dr. Samet reports that he spoke with Dr. Bill Bennett (CEMLB's dosimetry expert) to ask his impression of the results of both the PI's calculations and Dr. Miller's calculations. Dr. Samet reported Dr. Bennett was surprised that there was such close agreement. Dr. Samet believed that based on Dr. Bennett's and Dr. Bahman's calculations similar responses, Dr. Samet didn't feel that more independent analyses would change our level of comfort. Dr. Samet continued that a statistician could calculate the sample size needed to achieve statistical significance if we first provide answers to the following: 1. How variable is the data? 2. What level of significance are we trying to reach? 3. What value of discrepancy is biologically meaningful? Do the values between the PI's and CIIT's analysis have to be within 10%, 20%, or 200% of each other? Dr. Samet pointed out that CIIT's computer model does not represent the 'gold standard' against which the PI's calculations should be measured. Dr. Samet pointed out that generally experimentally-derived data trumps computer models. Dr. Samet asked where we should be heading if the numbers from both sources had agreed. If the answer was 'no,' then no further analysis was needed. If it is 'yes,' then he believed that the results are academic and possibly worthy of a published paper.

Dr. Birnbaum wrote to Dr. Zenick that she thought there might be some miscommunication on the credibility issue. She states that the values for the two subjects studied appeared to be accurate. She went on to ask if Dr. Zenick's concern is with two subjects not being enough, we could look into doing more with another PSC if Dr. Miller was willing.

After rereading Dr. Samet's comments, Dr. Birnbaum said that she thought we were ready to notify the IRB, then the subjects. She stated that more delay would not improve the situation or change the general conclusion that some of the subjects received approximately 50 times more particles in their lungs than they consented to. She went on to say that no one has been harmed and that also needs to be stressed.

Dr. Zenick wrote to Dr. Birnbaum that he thought Dr. Reiter should be involved and that an update briefing be set up for the following week (the week of March 25-29, 2002). He also stated that if it would be useful for someone from CIIT to be there and to please extend an invitation. Dr. Zenick addressed Dr. Samet's points stating that he was not looking for statistical significance, but rather something that would be credible to senior ORD management, the IRB, and others who may wish to question the calculations and the course of action to pursue. He stated that we will need to update the IRB, get their advice, and concur on the letter to the subjects.

3-22-02

Dr. Birnbaum recommended Dr. Seal contact the IRB to let them know what we have done, what the numbers are, how CIIT checked the numbers on two subjects and that they are in reasonable agreement with the PI's. She stated that if the IRB was satisfied, we could notify the subjects that they received more dose than they agreed to, but that there were no health effects. She believed that we should go ahead with the subject notification (once we are all satisfied with the letter).

Dr. Devlin wrote to Dr. Birnbaum that he had an opportunity to speak with Dr. Miller at the SOT meeting. According to Dr. Devlin, Dr. Miller was satisfied that the approach taken by the PI in calculating the dose delivered to the subjects was correct, because Dr. Miller used an entirely independent approach and arrived at the same result. Dr. Miller didn't expect the numbers he calculated to be identical with the PI's calculations, but they are within acceptable parameters. Dr. Miller didn't think that adding additional subjects to the analysis would increase the level of confidence in the PI's approach. Dr. Miller raised the issue of confidence in the PI's approach vs. confidence in the PI not making any mistakes in calculations. Dr. Miller indicated that trying to do an extensive QA on the PI's work would be beyond the capabilities of CIIT and would likely require a team of individuals. Dr. Devlin asked him if additional time and money would allow CIIT to accomplish this and Dr. Miller said that it would not. Dr. Devlin relates the example of a subject whose FRC is large for a person with mild COPD. Dr. Miller questions whether this value is correct. Dr. Devlin questioned the PI about this person's value to which the PI replied that there is a wide variation in persons with COPD and that this person's value is not out of line. Dr. Devlin asked the PI to prepare a table of his subject FRC's so that we could assess the degree of variability. Dr. Devlin went on to state that this issue does not relate to whether the PI's calculations are correct, but could be related to the QA question.

Dr. Devlin continued that one approach in the letter to the subjects is to indicate what the maximum dose they could be exposed to. Dr. Miller said that it is possible to identify those people with the highest theoretical dose and have EPA perform rigorous QA on just those few individuals. Dr. Devlin didn't know who could do the QA - whether Mr. Ray has the capability.

3-23-02 Dr. Birnbaum wrote to Dr. Devlin thanking him for the information and stating that she is quite convinced that we have enough information to move forward with notification of the subjects based on the PI's calculations and the analysis from CIIT. Dr. Birnbaum continued that QA had been previously discussed with Mr. Ray and he did not feel qualified. In addition, limited QA done early on in the investigation had found no problems.

3-25-02 Dr. Seal called Mr. Nelson to explain what we have done and to ask for advice as to subject notification letter.

4-09-02 NHEERL Senior Management briefed ORD Senior Management, Dr. Paul Gilman (ORD Assistant Administrator), Dr. Bill Farland (ORD Deputy Assistant Administrator for Science), Dr. Peter Preuss (ORD Human Studies Research Review Official) and Mr. Henry Longest II (ORD Deputy Assistant Administrator for Management).

4-15-02 Draft letter to the subjects e-mailed to attorney Mr. Tony Beyer of the Office of General Counsel (OGC) in Research Triangle Park.

4-17-02 Draft letter sent by Mr. Beyer to attorney Mr. David Lloyd of the OGC in Headquarters.

4-18-02 Draft letter sent by Mr. Lloyd to Mr. Beyer and Dr. Seal with some very constructive changes recommended.

Dr. Seal sent a copy of the draft of letter to the subjects to Dr. Roger Cortesi (ORD Senior Science Advisor) because he had not received the letter when it was sent as part of the briefing package.

4-19-02 Dr. Seal received a fax from Dr. Cortesi outlining four items which he and Dr. Preuss felt should be changed in the draft letter to the research subjects. They are:

1. "I think Zenick should sign"
2. "Should say by how much the exposure exceeded that in the protocol"
3. "Should you say on what basis the actual exposure is considered safe?"
4. "The "trust me" tone of the letter needs fixing"

These suggestions were sent by Dr. Seal to the NHEERL attendees of the briefing on April 9, 2002.

Dr. Seal received an e-mail reply from Dr. Zenick that he agreed that the letter dodged around the issue of how much exposure an individual received, and that if he were a subject it would probably be the first thing he would ask. He also stated that he realized what his initial reaction would be if he were told that the exposure

was 30 - 50 x. Dr. Zenick's message concludes that perhaps stronger information needs to be included showing that such exposures are in the "safe" range as used by others.

- 4-22-02 Dr. Seal prepared a draft of a briefing document and Q and A's for the Public Affairs officers.
- 4-29-02 Dr. Seal revised the letter to the research subjects incorporating three of the four recommendations of Dr. Cortesi and Dr. Preuss. The only change not incorporated was the "trust me" tone of the letter, which several people in NHEERL didn't feel was an issue. Dr. Zenick reviewed the letter and recommended that it be sent to Dr. Cortesi.
- 5-03-02 Dr. Seal received a telephone call from Dr. Cortesi stating that he was satisfied with the letter and was passing it along to Dr. Preuss. Dr. Cortesi stated that he believed that Dr. Preuss would also find the letter satisfactory.
- 5-07-02 Dr. Seal received notification that Dr. Preuss was satisfied with the letter. Because the content of the letter had changed from the draft reviewed by them earlier, copies of the most recent version were sent to Mr. Beyer in the Office of General Counsel and Dr. Steve Bernard, UNC IRB ,to update them and solicit their comments.
- 5-09-02 Draft letter sent from Dr. Reiter to Dr. Gilman for final review.
- 5-28-02 Dr. Zenick learned from Dr. Farland that Dr. Gilman had approved the draft letter, with changes, to the research subjects.
- 5-29-02 Dr. Vandenberg met with Dr. Zenick and learned that Dr. Gilman had approved the letter to the research subjects.
- 6-04-02 Final edits and individualization of the letters completed. Dr. Zenick's signature obtained on the final letters.
- 6-05-02 Finalization of the mailing including preparation of the 'return receipt requested envelopes.'
- 6-06-02 Letters mailed to subjects.
- 6-07-02 Received a voice mail message from subject J.H., (who is a nurse) who said that she had received the letter that day and wanted a chest x-ray.
- 6-10-02 Dr. Seal called subject J.H. back. She asked how this problem could have

occurred and Dr. Seal explained that the investigator changed the particle size and breathing pattern without recalculating the dose. Dr. Seal further explained that the problem was that the dose she had received was more than she had agreed to in the informed consent form, not that the dose she had received was likely to be toxic. Subject J.H. asked if anyone else had experienced problems and Dr. Seal told her that no one had. She again asked for a chest x-ray, and Dr. Seal suggested that a review of her case by a pulmonary physician might be a better place to start. A review with pulmonary function tests would indicate whether a chest x-ray was indicated. Dr. Seal expressed concern about unnecessary exposure to radiation. She asked if we could do a review of her pulmonary system including breathing tests and Dr. Seal told her that we would be glad to schedule such a review and offered to set up such an appointment. She said that she would call back to make an appointment.

Dr. Reiter called Dr. Seal asking about the date the first subject who received an excessive dose was exposed. Dr. Seal said that he would look into this and get back to him.

6-11-02

Because Dr. Seal in a timely manner could not find the data sheets that have the information on them about subject exposure dates (the individuals who have them are on leave or are out sick), he contacted Dr. Reiter by e-mail to let him know there would be a delay until they are located.

Dr. Cortesi spoke with Dr. Seal and told him that he had spoken with Dr. Greg Koski, Director of Office for Human Research Protection (OHRP). Dr. Koski made several recommendations to Dr. Cortesi:

1. Notify the IRB - (this was done on the day the incident was discovered and there has been a continuing written and verbal dialog since.)
2. Have the IRB review the letter to the subjects - (this was done on the initial draft of the letter as well as on a much later draft since the content had changed considerably as a result of subsequent reviews.)
3. Report the incident to OHRP - it is uncertain at this time whether this has been done, but Dr. Seal would contact the IRB and make this recommendation if it has not been done.
4. Did not recommend an investigation by the IG.
5. Recommended investigation by outside group be initiated promptly.
6. Dr. Koski indicated that he was more than willing to help in any way.

Dr. Seal called Dr. Devlin who is acting HSD Division Director and left a message that he would like to inform Dr. Devlin about Dr. Koski's recommendations.

Subject T.W. called to say that he had received a letter and he wanted to know if it was more than an effort to "protect your rear." Dr. Seal assured him that the purpose of the letter was to let him and other subjects know that an error in dose occurred and that although the dose of material was greater than specified in the informed consent form, it was similar in size to that used in other human and animal studies without harm. Dr. Seal continued to inform him that the purpose of the letter was full disclosure, because we thought it was the right thing to do and because we wanted subjects to know in the unlikely case that there were future medical problems. Dr. Seal asked if he had experienced any problems since his participation (1996) and he said that his asthma had remained about the same since then. Dr. Seal reassured him that he could call at any time if he wished to discuss the incident further.

6-12-02

Dr. Zenick called Dr. Seal to convey two messages: He expected the dose information to be sent to Headquarters by Dr. Devlin and he wanted all of the amendments to the PI's study to see if there was information in those about dose calculations.

Dr. Vandenberg met with Dr. Seal for an update. He emphasized that responding to requests for information about the PI incident had the highest priority, and that he expected Dr. Devlin to respond with dose information as requested by Dr. Zenick.

Dr. Seal met with Mr. Nelson, Director of the UNC IRB about a Federal Wide Assurance for the Human Studies Division. Dr. Seal mentioned the contact Dr. Cortesi had yesterday with Dr. Koski and his recommendations, some of which directly affected the IRB. Mr. Nelson asked for a list of Dr. Koski's recommendations with copies to Dr. Robert Lowman (UNC Director of Research Services), and attorney Ms. Susan Ehringhaus (UNC Senior Counsel). Mr. Nelson also asked for the chronology of events in this incident, but Dr. Seal told him that it contained information covered by the Federal Privacy Act, such as discussions of disciplinary measures against the investigator, and for that reason was not likely to be released unless heavily redacted. Dr. Seal also asked for the opportunity to compare the IRB files of amendments with his own to be sure it was complete and Mr. Nelson agreed to this request.

Dr. Seal sent an e-mail to Dr. Devlin explaining that the date (1998) cited as the first date that a subject received an excessive dose was incorrect. A careful review of the subject data indicates that the first exceedence was on March 13, 1996. Dr. Seal suggested that Dr. Devlin forward the correction up the chain of command, with the recommendation that amended briefing statements be sent out with the correct information.

Dr. Seal informed Dr. Devlin that both Dr. Vandenberg and Dr. Zenick wanted the subject dose information delivered to Headquarters by the end of the day.

Dr. Seal drafted the letter Mr. Nelson had requested outlining Dr. Koski's recommendations, explaining why he couldn't release the chronology of events, and reassuring the UNC officials of the EPA's continuing cooperation with the university through to a satisfactory resolution. In addition to sending copies to Dr. Lowman and Ms. Ehringhaus, Dr. Seal sent copies to Dr. Vandenberg, Dr. Zenick, and Dr. Reiter to keep NHEERL management apprized.

Mr. Richard David from the Assistant Administrator's (AA) office called with questions:

1. When was the last subject studied? (Dr. Seal didn't have the answer for this question, but told Mr. David that he would check the record and call him back)
2. Who discovered the problem? (A post doc in the principal investigator's laboratory.)
3. How many subjects have called in response to the letter? (Two)
4. Where were the subjects from? (74 were from Eastern North Carolina, one was from South Carolina.)

Mr. David also mentioned the problem start date as 1998, and he was told that was an error that the problem occurred first on March 13, 1996, and that we were in the process of correcting the error.

Dr. Seal called Mr. David to tell him that the last subject studied was on February 15, 2001.

Dr. Seal delivered the package of research papers prepared by Dr. Devlin describing the safety of the dose to the subjects to Dr. Zenick's office.

By e-mail, Mr. Nelson requested a copy of the final version of the letter to the research subjects. Dr. Seal found the message the following morning in his in box and sent him a hard copy of the letter.

6-13-02

Dr. Seal called Ms. Ann Brown (NHEERL's Public Relations Coordinator) to tell her that he had discovered a discrepancy in the years cited in some of the documents intended to provide information to the media and the public. She asked him to revise the documents and send the revisions to her. She said that she would distribute the revised documents to the appropriate individuals in the Agency.

Dr. Seal told Dr. Devlin that he had contacted Ms. Brown about the error in date

because none of us wanted any error to get to the public or the media. Dr. Devlin concurred in this decision.

In response to a request from Dr. Zenick earlier in the week, Dr. Seal delivered to Dr. Devlin for forwarding to Dr. Zenick a package containing all of the amendment requests and amendment approvals for the study. This information was derived from records in the Division files, the Medical Station files, and from the IRB files.

6-17-02 Dr. Seal reviewed the messages on the toll-free telephone and found two. The first was from subject J.H. who said that she was going on vacation on June 29, 2002 and would not be back until after July 1, 2002. When she returns, she would like to schedule an examination by one of the EPA pulmonologists.

Subject J.W.D called, leaving a message wanting to know what symptoms he should expect if he was going to have problems as a result of his participation.

6-18-02 Dr. Seal called subject J.W.D. but was able only to leave a voice mail message that he would try to call again.

Dr. Seal again called subject J.W.D. and again was only able to leave a voice mail message that he would continue to try to reach him.

6-19-02 Dr. Seal again called subject J.W.D. and spoke with him. Dr. Seal explained that the symptoms he would likely have experienced would be shortness of breath and cough, but that these would likely have been experienced in the days to weeks after participation rather than months to years, and that it was highly unlikely that he would experience any symptoms so far removed from the exposure. Subject J.W.D. seemed satisfied with the explanation of symptoms and their time course. He did ask how this error occurred and Dr. Seal explained that the investigator had changed the particle size and breathing patterns without recalculating the dose, that he was looking at deposition fraction (Dr. Seal explained what deposition fraction was and how it differed from dose). The conversation ended with Dr. Seal offering to answer any additional questions subject J.W.D. might have in the future, and with thanks for the subject's participation in HSD research.

Mr. David called and left a voice mail message asking for the number of subjects who had responded to the letters.

6-20-02 Dr. Seal retrieved Mr. David's message and called him giving the same information that was being passed through line management. Dr. Seal also told Mr. David that the information should be relayed to the AA's office per Dr. Cortesi's request of several days ago. Mr. David seemed satisfied.

- 6-26-02 Ms. Lori Graham, Division Secretary, sent a fax to Ms. Joan Pendergraph, of the UNC-Chapel Hill General Alumni Association asking for assistance in locating subjects who were students at the time and who have moved. A list of the students for whom notification letters were returned was attached to the fax.
- 6-27-02 Dr. Vandenberg wrote a note to Dr. Reiter and Dr. Zenick explaining that only three subjects had called in on the toll-free number. He asked if, instead of daily notification of activity, whether it would be acceptable for the Division to notify only in the case of activity. Dr. Vandenberg also summarized the subject response to the letters to date: 28 letters have been accepted, 22 letters are pending with no response, and 25 letters have been returned undelivered.
- 7-1/6-02 While on vacation, Dr. Seal checked his voice mail for calls from subjects. There were none.
- 7-10-02 Addresses for 14 subjects whose original letters were returned as undeliverable were obtained from the UNC Alumni Association and second letters to these individuals were sent on this date.
- 7-1-7-02 Subject M.M. called in response to the second set of mailings (the first letter for this subject came back undeliverable and a current address for her was obtained from the University of North Carolina Alumni Association). She was concerned about side effects of sebacate oil. She had already looked it up on the Internet and found that it caused effects only at extremely high doses. Dr. Seal assured her that more than six years after study (she participated in March 1996), it was highly unlikely that she would experience any side effects. She was confused about her participation in the study and about the dates of her participation, so Dr. Seal offered to double check this information in her records and get back to her.
- After confirming subject M.M.'s participation and the dates that she was a subject in these studies, Dr. Seal called subject M.M. and confirmed her participation and the dates of study for her. She asked for copies of the consent form and Dr. Seal offered additionally to copy a card which has all of her participation in HSD studies on it. She also asked for copies of journal articles. Dr. Seal got a reprint of an article from the principal investigator. Dr. Seal sent subject M.M. a copy of her signed and dated consent form, her log of participation in EPA studies, the reprint of the journal article and a cover letter offering to discuss her concerns at any time in the future.
- 7-23-02 Subject D.B. said that he had received his notification letter on June 6, but was away. The letter had finally come to the surface in the subject's "to do" box and he was calling to ask what the symptoms would be. Dr. Seal told him that the most likely symptoms would be cough and shortness of breath. The subject told

Dr. Seal that he has had cough for several years and has been seen in the UNC ENT clinic and treated chronically with Halitussin. Subject D.B. asked if the sebacate oil might have triggered the cough. Dr. Seal told him that this would be unlikely but could not be ruled out entirely. Dr. Seal suggested that subject D.B. check with the ENT clinic to determine from their records when the cough began (preceding or following, and by how much?) with respect to the subject's participation in the EPA study. The subject also asked if the sebacate oil might have triggered an underlying problem that the subject already had. Dr. Seal said that this was possible, but again he didn't think very likely. Dr. Seal offered to make the subject's medical records available to the subject or his care givers and asked to be kept apprized of the subject's investigation into his condition. Dr. Seal offered to speak with the subject at any time and thanked him for calling.

7-26-02

Dr. Seal began preparation of the documents for the independent review.

Dr. Seal reviewed the IRB files and compared them against the Division files in preparation for the independent review. There were a few items missing from the Division files that the IRB staff let him copy for the Division records.

Problems Identified and Solutions Considered in Response to Protocol Violation in 2001

Background:

In the United States, human research subject protection is based on three elements: Knowledge of the regulations, trust that the regulations will be followed, and disciplinary measures when the regulations have been violated. In general the former two elements have greater application to human research because the latter is used only in extreme situations of violation. From top to bottom in the human research enterprise, these principles are applied. The Office of Human Research Protections (OHRP) educates, as well as depending on other qualified bodies (e.g., IRBs) to educate the human investigator. OHRP also trusts the IRB, and the IRBs trust the investigators to follow regulations and to not deviate from them. Only when there is a significant violation of the regulations does the third element, discipline, come into play.

Problem: Protocols which over a period of time metamorphose into different protocols as a result of being amended numerous times.

Resolution: All amendments will be reviewed by the Branch Chief, Division Director, NHEERL Human Subjects Review Official and the HSD QA Officer before they are submitted to the IRB. Any amendment which changes the fundamental nature of the original protocol will not be allowed to be sent to the IRB. Instead, a new protocol will need to be prepared and processed through the usual approval process.

Problem: Not all informed consent forms being signed.

Resolution: New subject study charts will be reviewed for completeness once per month, in order to assure any noncompliance is quickly corrected if it occurs.

Problem: Investigators being added to protocols with notification of the IRB

Resolution: Before a new investigator is added to a protocol, an amendment to the protocol will be prepared, and all amendments will require management review before they are sent to the IRB. This is important because when a new investigator is added to a protocol, proof that the individual has taken the required education must accompany the notification. This is the only way that the IRB knows whether the required education has been completed.

Problem: Information is not getting to those who need it.

Resolution: Copies of letters, approval memos, approved protocols, amendment letters, adverse event reports, and informed consent forms will be distributed to their Branch Chief, Division Director, the QA Officer, and the NHEERL Human Subjects Research Review Official, the Medical Station, and Subject Recruitment. Old versions of documents (e.g., consent forms) should be shredded. Information of this type should also be placed on the shared drive.

Problem: Potential lapses in subject advocacy.

Resolution: Traditionally the nursing staff has been the advocate for subject safety and welfare, roles that should not change. However, subject safety and welfare are the responsibility of every employee in the HSD. Employees should be encouraged to bring to the attention of the NHEERL Human Subjects Research Review Official and/or the Division Director any concerns about research subject safety and welfare. Such notification can be with the reporting individual's identity known or anonymously.

Problem: The perception, real or imagined, that line management is not as consistent in the matter of subject safety as they should be.

Resolution: This issue has already received aggressive attention. There have been two meetings devoted to alertness training, the first involved investigators, the second, the entire HSD staff. In addition, there is an open door policy in the offices of both the Division Director and for the NHEERL Human Subjects Research Review Official to encourage members of the Division to come forward with subject-related issues. An anonymous box for leaving subject safety items has also been established. Subject safety issues raised by anyone in the Division should receive prompt and decisive review by line managers.

Problem: Additional peer review of new protocols.

Resolution: In the past, two peer reviews of a new protocol were required. In order to strengthen peer review as well as increase interaction among the staff, the protocol will be presented at a meeting of investigators and medical staff and feedback from all in attendance will be sought, which is expected to yield a stronger review.

Problem: Studies in which the chamber support contractor does not have a role, do not have enough oversight to prevent errors.

Resolution: In the future, there will be audits on a yearly basis by in-house staff to provide additional oversight in order to catch possible errors in dosing and other noncompliance with the protocol. UNC studies with EPA collaborators would be audited in the same way. A qualified pharmaceutical scientist will review the preparation of material intended for administration to human subjects.

Problem: New investigators don't know what is expected of them in the Human Studies Division

Resolution: In order for new investigators to learn the "culture" of the Division, each new investigator will be coupled with a mentor, a seasoned investigator who knows the expectations of performing human research, and will be a co-investigator for at least one study, or until the mentor feels that the new investigator can handle a human study independently. The appointment of mentors for new investigators will be done by the Branch Chiefs.

Problem: All investigators and support personnel sometimes unsure of their roles on a new study.

Resolution: Before a study can begin, the principal investigator will convene a meeting of all personnel involved in the study (co-investigators, subject recruitment, chamber support, and medical station staff) to review the study, and answer any last minute questions.

Problem: Studies beginning without a clear idea of the logistics of the operation of the study.

Resolution: A "dry run" of each study will be conducted to allow visualization and timing of the events that take place during the execution of the protocol for the first time. Members of the staff can stand in for research subjects.

Although the protocol review and implementation process undergoes constant review and upgrading, we believe that these additional measures at this time provide additional real safeguards for the welfare and safety of our human research subjects.

**ASSURING HUMAN
SUBJECT PROTECTION IN
CLINICAL STUDIES**

April 9, 2002



NHEERL



HUMAN Subjects Briefing – Main Points

- Study to measure pulmonary deposition of various sized inert wax particles in healthy and susceptible populations
- Dosage of inhaled particles exceeded protocol
- Study terminated immediately; PI barred from additional clinical research indefinitely
- IRB notified
- No subject reported ill effects
- Dose calculations and external verification suggest minimal risk
- Corrective actions implemented to avoid recurrence

PROBLEM STUDY

- A “dose” as contrasted with an “effects” study
- Study Purpose: Human volunteers exposed to inert wax particles of various sizes to define where different sized particles deposit in the lung

PROTOCOL VIOLATION

- It was discovered in August, 2001 that the mass of particles given to some subjects was considerably greater than specified in the human research protocol

Vulnerabilities:

- Inattentive Investigator
- Project fell outside the scope of rigorous contractor QA review that is applied for pollutant delivery for “chamber studies”
- Numerous, IRB-approved protocol amendments w/o adequate internal review

IMMEDIATE ACTIONS TAKEN

- All studies by the EPA Investigator immediately suspended indefinitely
- The Institutional Review Board (UNC) notified of the incident the same day; continued engagement throughout period of corrective actions
- Pulmonary physicians and experts in dosimetry consulted to determine likelihood of harm to any of the subjects
- Literature reviewed to determine if health effects were reported in other studies of animals or humans exposed to these waxy particles used in this study
- Conclusion was that it was very unlikely that the doses used in this study could have resulted in any harmful effects to the volunteer

ADDITIONAL ACTIONS TAKEN

- Disciplinary actions taken against EPA investigator and settlement in late December
- EPA investigator completed the calculation of the dose of particles delivered to each subject in February
- This approach to estimate dose to each subject was validated by outside experts in March
- Conclusion: No harm has been done to the subjects
- Following further consultation with and approval from the IRB and legal counsel, subjects will now be notified by letter and given an "800" number for questions and concerns

CORRECTIVE ACTIONS TO AVOID RECURRENCE

- Conduct broad vulnerability analysis
- Records of all other HSD investigators' studies were reviewed; no violations uncovered in any other study
- Stricter management review of ongoing protocols and amendments; protocols now limited to a maximum of 5 years
- Outside Quality Assurance - Independent contractor to oversee delivery of pollutants in all studies
- Formal empowerment of nurses as subject advocates, including daily confirmation of signed consent forms

CORRECTIVE ACTIONS TO AVOID RECURRENCE (cont'd)

- Enhanced training of staff will be provided through:
 - regular investigator meetings to review policies on human studies
 - coupling new investigators with mentors and having new investigators serve as co-investigators before conducting human research independently

Additional Protocol Violations

- 18 of 118 subject consent forms lacked the signature of the EPA investigator; one lacked signature of research subject

Vulnerability

- Inattention by investigator

BOTTOM LINE

Isolated incident occurred



Appropriate decision and
corrective action

Broad vulnerability
assessment



Improved policies and
procedures to assure
protection of human
subjects

1. **Date of Application:** September 1, 1991
2. **Title of Project:** Determination of Deposition Dose of Inhaled Particles in Human Lung Airways
3. **Principal Investigator:** Chong S. Kim, Ph.D.
Clinical Research Branch, U.S. EPA/
Department of Medicine
UNC-Chapel Hill
4. **Co-investigators:** Shu-Chieh Hu, Ph.D.
Center for Environmental Medicine and
Lung Biology, Department of Medicine,
UNC-Chapel Hill

Timothy R. Gerrity, Ph.D.
Howard Kehrl, M.D.
Clinical Research Branch, U.S. EPA/
Department of Medicine
UNC-Chapel Hill
5. **Granting Agency or Sponsor:** U.S. EPA and Center for
Environmental Medicine and Lung
Biology, Department of Medicine,
UNC-Chapel Hill

6. Purpose and Rationale:

Purpose: The purpose of this study is to investigate deposition dose of inhaled particles at local regions of the conducting airways and factors affecting the deposition.

Rationale: Because of differences in anatomical structures and flow patterns, deposition of inhaled particles vary locally within the lung. This often causes a tissue injury and/or initiation of disease processes at local sites that receive high particle doses (1), while the average lung dose is still in the acceptable range. The enhanced local deposition is particularly evident in the carina of the conducting airways (2) and airway model experiments suggest that deposition dose near the carina would be orders of magnitude higher than the average airway dose (3,4). Despite the complexity of airway geometry and flow characteristics, airway deposition is often assessed using simplified models that lack the reality of airway flows and tend to underestimate the significance of airway deposition of inhaled particles. Airway deposition in vivo, however, has not been rigorously investigated. Current knowledge is based on the premise that particles deposited in the conducting airways are cleared from the lung within 24 hours by mucociliary mechanism. Airway deposition is therefore assessed indirectly by measuring total lung deposition immediately and 24 hours after inhalation of radiolabelled particles (5). In this method regional variations within the airways can not be assessed. Further, the 24-hour dividing line for the airway deposition is often questioned (6). A direct measurement of airway deposition is thus needed.

7. Outline of the Study:

Deposition fraction of inhaled particles will be measured in 20 healthy, young (18-40 years in age), non-smoking volunteers (10 males and 10 females). Test particles of 3 μm diameter (particle size may vary between 1 and 5 micron) will be generated by condensing di-2-ethylhexyl sebacate oil vapor on sodium chloride nuclei and a small bolus of the aerosol (70 ml) will be delivered to specific regions of the airways. The subject will first breathe in clean air at a controlled flow rate: either 125, 250, and 500 cm/s with a tidal volume of 500 cm^3 , or 250, 500 and 1000 cm/s with a tidal volume of 1000 cm^3 or both from the functional residual capacity and without pause breathe out to the residual lung volume. During the breathing maneuver, airflow will be monitored continuously by means of a pneumotachograph and flow signals will be processed with a Dell 325 personal computer on-line. An aerosol bolus will be released into the inspiratory stream in such a way that penetration of the bolus into the lung will be 100, 150, 200 and 250 cm^3 which may represent the proximal, middle, and distal airway regions, respectively. Timing of the bolus delivery will be fully automated in conjunction with the computer. Aerosol concentration of the bolus will be monitored with a laser aerosol photometer and signals will be analyzed with the personal computer to calculate the total quantity of inhaled and exhaled aerosols and subsequently deposition fractions, $DF = (\text{inhaled} - \text{exhaled})/\text{inhaled}$ aerosol. For a given test setting, three repetitive measurements will be made. A sequence of aerosol deposition measurements will be performed in normal subjects after pulmonary function tests including spirometry and body plethysmography. The aerosol bolus technique has been used successfully in our previous studies (7) and by other investigators (8-11).

After the measurements in the normal lung conditions, the subject will be challenged with methacholine or histamine aerosols (see below for challenge procedures) and a few selected measurements will be repeated immediately, 30 and 60 min after the challenges. Both of the challenging agents cause airways constriction. However, the constrictive action of methacholine is mainly in the large airways, whereas the histamine effect is primarily in the middle and small airways. Responsiveness of aerosol deposition to changes in airway dimension may therefore be assessed after the challenges. In this protocol, because of a short period of time available for measurements, one pulmonary function (sRaw) will be measured after the challenge. Bolus aerosol deposition will be measured for four different delivery depths as used in the pre-challenge measurements but with one selected breathing pattern (i.e., 500 ml (or 1000 ml) tidal volume and 500 cm/s flow velocity). Airway challenges with methacholine and histamine will be performed on separate days at least a week apart to minimize a cross interference: therefore, the same subject will make two separate visits to complete the study.

Body plethysmography: The subject will sit in a constant

volume body box and perform a brief (~20 sec) panting maneuver against both an open and closed shutter for the measurement of airway resistance (R_{aw}) and thoracic gas volume (TGV). The specific airway resistance (sR_{aw}) will then be determined by the formula, $sR_{aw} = R_{aw} \times TGV$.

Spirometry: The subject will inhale to the maximum lung capacity and exhale rapidly and completely into a rolling seal spirometer. From this maneuver, the forced vital capacity (FVC), forced expiratory flow in one second (FEV₁), maximal expiratory flows at 25, 50 and 75% of VC, and the ratio FEV₁/FVC will be measured.

Airway challenge: The subject will inhale sequentially at 5 min intervals 5 breaths of methacholine aerosols generated with doubling concentrations of methacholine in buffered saline; the sequential concentrations will be 0.0 (saline), 1.25, 2.5, 5.0, 10.0, 20.0 mg/ml. Aerosols will be generated with a Devilbiss air jet nebulizer operated at 20 psi air pressure and delivered during the inspiratory phase by means of a breath actuated valve system. Two measurements of specific airway resistance will be made 2 min after every inhalation until a 100% increase from baseline values is reached. Histamine aerosol challenge will be performed in the exact same way as the methacholine aerosol. If the value of sR_{aw} is not reached to a 100% increase from the baseline after airway challenge with a 20 mg/ml solution, no further challenge will be made and the subject will be disqualified for the study. This procedure is closely in line with the recommendations of the Subcommittee on Bronchial Inhalation Challenges, Assembly of Allergy and Clinical Immunology (12) and National Institute of Allergic and infectious Diseases (13).

Test aerosols: Three micron size oil particles will be generated by condensing oil vapor (di-2-ethylhexyl sebacate) on sodium chloride nuclei by means of evaporation-condensation techniques. Particle concentration will be in the range of 10,000 particles/cm³. Because aerosol will be inhaled as a bolus of 70 cm³ volume, total aerosol mass to be inhaled will be in the range of 10 µg per inhalation. The sebacate oil is highly stable and nonhygroscopic and has been used in human studies for a decade (8,10,11,14,15).

Data collection and analysis: Respiratory flow rate, respiratory time, and aerosol concentration will be monitored and the data will be processed on line with a dedicated personal computer. Particle deposition fraction will be calculated as a function of delivery depth of aerosol bolus and inspiratory flow rate.

8. Duration of Study and Duration of Subject's Participation:

The study will begin in the Fall of 1991 and will take about six months to complete. Each subject is required to make two

separate visits to our laboratory and each visit will require about five hours of time.

9. Subjects:

Ten healthy male and 10 healthy female non-smoking subjects between the ages of 18-40 years will be recruited from the population in and around Chapel Hill, NC. All potential subjects will undergo a screening procedure which includes the Minnesota Multiphasic Psychological Inventory (MMPI), complete medical history, physical examination, SMA-20 blood chemistry screen and a complete blood count (CBC) with differential. Black subjects will be screened for sickle cell disease; presence of sickle cell disease will result in exclusion from the study. Female subjects will be asked to provide a menstrual history and provide a urine specimen for pregnancy testing. Females believed to be pregnant will not be accepted into the study. To be included in this study, the subjects must also meet the following criteria:

1. No history of smoking within 1 year, and no history of more than 0.2 pack years prior to that.
2. No history of recreation drug use by inhalation within six months, and no history of recreational drug use by inhalation that regularly exceeded once per week prior to that.
3. No history of acute or chronic cardio-respiratory disease.
4. No personal history of hay fever or asthma.
5. No history compatible with acute respiratory infection of viral illness within the previous four weeks.
6. FVC > 80% of predicted normal value.
7. FEV₁/FVC > 75% of predicted normal value.
8. Raw < 2 cm H₂O/l/s.

Accepted subjects will participate in a training session. Training session will consist of instruction in the performance of spirometry and body plethysmography and the maintenance of consistent breathing pattern (flow rate and tidal volume) for the aerosol inhalation. Subjects may be excluded from further participation in the study on the basis of inadequate performance of the pulmonary function tests or the inability to maintain a controlled inhalation of aerosol.

The test subjects will be recruited for this study by Bionetics Inc., under contract to the EPA. The majority of the subjects will be students and/or faculty-staff of the local universities. All subjects and potential subjects who have not completed the screening procedure and routine physical examination within the previous year will receive \$20.00 when they complete these. Subjects accepted into the protocol will be paid \$10.00 per hour during the testing period. In addition, a bonus of \$10.00 will be paid for arriving on time.

10. Anticipated Benefits to Subjects and/or Society:

Subjects will receive a complete medical examination free of charge and the results of the exam will be accessible to the subjects. Subjects will receive a payment for participating in the study.

11. Risks to Subjects and Safeguards to Minimize Risks:

Pulmonary function tests including spirometry and body plethysmography have little or no risk to the subject. During the initial physical exam, there is a possibility of a small hematoma or swelling developing at the site of blood sample collection.

Bronchial challenges with methacholine or histamine aerosols are routinely used clinically for the diagnostic purposes and the procedure has been standardized (12,13). Methacholine is a chemical analog of the natural, endogenous bronchoconstrictor, acetylcholine. Histamine is also the natural, endogenous bronchoconstrictor. Therefore, both methacholine and histamine aerosols cause a narrowing of the airways and this may cause a feeling of "tightness" in the chest or shortness of breath. In addition, histamine may cause flushing, rapid heartbeat or mild headache, all of which are transient. The effects are usually reversed spontaneously in about one hour (16). The bronchoconstrictive response to methacholine or histamine aerosol is usually negligible in normal subjects at doses below 1 mg/ml solution aerosol (5 breath inhalation) (17). Therefore, a solution of 1.25 mg/ml will be used as a starting concentration. However, the challenge is controlled carefully and allows small, stepwise increases in bronchoconstriction monitored by the measurement of sRaw. An airway narrowing to the level of a 100% increase in sRaw does not pose any risk to the subject. However, the airway challenge will be terminated at any point during the procedure if an unwarranted discomfort, risk or anxiety is present or if the subject asks to discontinue for any reason. A bronchodilator drug (i.e., metaproterenol) will also be offered to the subject to reverse the effects of the challenge aerosols quickly.

Inhalation of bolus aerosols (di-2-ethylhexyl sebacate oil, DEHS) will have a minimal risk to the subject. DEHS oil will be used because 1) the aerosol has been used for inhalation studies in humans over a decade and there has been no report of adverse health effects (8-11,14,15) and 2) DEHS is highly stable at high temperature and suitable for generation of large size particles (i.e., 3 μ m diameter) by a condensation technique. DEHS is used as a plasticizer for elastomers and also used as a synthetic lubricant for jet engines. In France and Italy, DEHS is permitted for use in plastics that may come in contact with foodstuffs. There are a limited number of toxicological studies for DEHS but all of them show negative toxic effect (18).

Skin exposure studies conducted by Mallette et al (19) showed no irritation reactions in both animals and human subjects after the standard patch tests with 100% concentration of DEHS. A repeated tests for a period of two weeks did not show any signs of

sensitization. An intraperitoneal injection of 6 gram/kg DEHS showed no signs of pathological changes after one month of observation in rats (19). The intraperitoneal and oral LD50 values for rats and mouse was found between 12.8 and 25.6 g/kg of body weight, indicating a low level of oral and peritoneal toxicity (20). Swift et al. studied rats after a 4-hour exposure to 0.25-250 mg/m³ DEHS aerosol and they found no pulmonary and systemic effects (18). In this proposed study, the subject will inhale DEHS bolus aerosol (10 µg per bolus) about fifty breaths during a test day; therefore, total inhaled dose will be about 0.5 mg. However, because only a fraction of the inhaled particles (<10%) are expected to be deposited in the airways, the actual total tissue dose will be < 50 µg. This dose is about 20 times below the dose tested in animals at which there was no harmful effect found.

12. Informed Consent:

Informed consent will be obtained from the subjects after the purpose and procedures of the study and the potential risks from participation are explained. Each subject will then be asked to read a statement of informed consent. After ample opportunity to have any questions answered, the subject will sign the Informed Consent Form.

13. Costs to be Borne by Subjects: None

14. Use of Radioactive Materials: None

15. Statement of Agreements:

The Principal Investigator, whose signature appears below agrees to a continuing exchange of information or advice with the committee on the Protection of the Rights of Human subjects.

The Principal Investigator agrees to communicate with the Committee to obtain its approval before institution of any significant change or addition to the project or before continuing beyond the expiration date.

The Principal Investigator agrees to inform the Committee and Hospital Risk Management upon the occurrence of any previously unsuspected or serious adverse effects or complications.

The Principal Investigator agrees to provide each subject with a copy of the signed consent form and to keep the original of the signed consent form in the subject's file.

Signature of P.I.

References

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BRIEF SUMMARY OF PROPOSAL

HR-5

Title: Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D.

Note:

1. This summary will be read by all committee members including lay members. It must be written using language and technology they can understand.
2. The summary should be succinct (100 - 400 words) and limited to the space allotted below:
3. Include: purpose and rationale (question to be answered by the research); number, age and sex of subjects; duration; research method employed; method of data analysis
4. If complex chemotherapy or other regimen is involved, submit a simplified summary diagram of experimental design on a separate page.

Deposition pattern of inhaled particles in the lung is usually inhomogeneous and this often causes an excessive tissue burden at local areas while the average lung dose is still in the acceptable range. One such area is the conducting airways. Because of the unique branching geometry, airway deposition is highly irregular and the sites of high deposition often coincide with the sites of bronchial tumor. However, experimental data that are specific for airway deposition in vivo are not currently available and theoretical models usually lack the reality of airway flows and underestimate the significance of particle deposition in the airways. The purpose of the present study is therefore to measure particle deposition in the airways of the normal lung and of the lungs with altered airway geometry. Twenty healthy young (age = 18-40 years) volunteers (10 males and 10 females) will be studied. The subject will be asked to breathe clean air with a controlled breathing pattern and a bolus of aerosol (70 ml) will be delivered to the airways. The aerosol bolus will be delivered to three different depths into the airway with a help of an on-line computer: proximal, middle and distal segment of the airways. Total amount of aerosol inhaled and exhaled will be monitored in situ near the mouth with a laser aerosol detector and particle deposition will be determined by the difference between the inhaled and exhaled aerosols. Deposition measurement will be repeated with different breathing patterns: shallow vs deep and slow vs fast breathing. The measurements will also be made after the subject will have inhaled pharmacologic agents (methacholine and histamine) that cause airway constriction. The subject will have two visits to the laboratory at least a week apart and each visit will take about 5 hours.

BRIEF SUMMARY OF PROPOSAL

HR-5
August 5, 1996

TITLE: Determination of deposition dose of inhaled particles in the human lung airways.

PRINCIPAL INVESTIGATOR: Chong S. Kim, Ph.D., US EPA/NHEERL/HSD and
School of Medicine, UNC-CH

1. **Purpose of study:** The purpose of this study is to investigate deposition dose of inhaled particles at local regions of the lung and factors affecting the deposition. We will investigate differences in lung deposition in four different subject groups including normals, heavy smokers, asthmatics, and COPDs and between male and female.

2. **Brief description of experimental design, including what will be asked of/done to subjects:**
The subject will first breathe in clean air at a controlled flow rate of 125, 250, and 500 cm³/s with a tidal volume of 500 ml from the functional residual capacity and breathe out to the residual lung volume. During the breathing maneuver, an aerosol bolus (~40 ml volume) will be injected into the inspiratory stream in such a way that the bolus penetrates into a specific volumetric depth into the lung (from 50 to 500 ml with an increment of 50 ml). Aerosol concentration of the bolus will be monitored *in situ* with a laser aerosol photometer at the mouth and signals will be analyzed to calculate the total as well as regional deposition of particles. At the end of the bolus inhalation the subject will inhale the same aerosol with a whole tidal volume and total lung deposition will be determined. Two different groups of aerosol, coarse (1-5 μ m diameter range) and fine particles (0.05-0.5 μ m diameter range) will be tested. The standard pulmonary function tests including spirometry, body plethysmography and single-breath nitrogen washout test will be performed for each subject prior to aerosol inhalation.

3. **Number of subject** 160 ; **Duration of individual subjects involvement** 3 days ;
Duration of study 3 years ;

a. **How are subjects recruited?** Subjects will be recruited by Bionetics Inc. under contract to the EPA. *chain of command*

b. **Restrictions or exclusions:** All subjects: No acute respiratory infection of viral illness within the previous four weeks, no recreation drug use by inhalation within 3 months.

N=20 - Normals: no history of smoking within 3 year. FEV₁/FVC > 70%.

Old people: age > 60 years, No history of smoking within 3 years, 60% < FEV₁/FVC < 70%.

Smokers: at least 1 pack/day for at least last 5 consecutive years.

Asthmatics: proven medical history and physician's diagnosis, FEV₁/FVC > 60%.

COPD: proven medical history and physician's diagnosis, FEV₁ > 40% Pr, FEV₁/FVC > 40%.

c. **Inducements:** A payment of \$10.00 per hour during the study and additional \$10.00 as a bonus for arriving promptly at the appointed time. A \$10.00 bonus for completing three day visit. A payment of \$20.00 for the initial screening and physical examination.

4. **Benefits:** to subjects: A complete medical examination free of charge. Subjects will receive a payment for participating in the study.
to society: New data to be used to improve health risk assessment for inhaled pollutant particles.

5. **Risks to subjects (drugs, devices, venipuncture, confidentiality, other):**
No drugs and no unusual devices. Minimal risk with venipuncture. Confidential data storage.

6. **Measures to minimize risks:** Nurses and physicians on duty on site.

7. **Costs to subjects (transportation, drugs, devices, labs, physician fees, others):** None.

**Determination of Deposition Dose of Inhaled Particles
in Human Lung Airways**

IRP No. NHEERL-H/HSD/CRB/CSK/92-004-002¹₁

ORD Subcomponent: H29001

QA Category II

Protocol Approval

Branch Chief: Robert J. Davoli Date: 9/16/96

QA Manager: Michael Ray Date: 9/30/96

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1. Introduction

Deposition dose and site of inhaled particles within the lung are one of the key determinants in health risk assessment of particulate pollutants. Previous lung deposition studies have dealt largely with total lung deposition measurement, and a body of data has been reported for normal subjects with respect to particle size and the mode of inhalation (1-4). Those studies have shown that total lung deposition varies widely depending on particle size and breathing pattern; namely, the larger the particle size for particles $> 0.5 \mu\text{m}$ diameter or the smaller the particle size for particles $< 0.5 \mu\text{m}$ diameter, the greater the lung deposition. However, because particle deposition does not take place uniformly throughout the lung, there exist local regions of the lung at which deposition dose exceeds the average lung dose (5,6). It is also anticipated that local deposition varies to a much greater extent than total lung deposition, which may result in incidents of extreme dose enhancement at local regions. This may have significant implications in health risk assessment because a high local dose may cause tissue injuries and/or initiate a disease process (7), while the average lung dose is still in the acceptable range. The information on detailed regional lung deposition is currently lacking. Furthermore, despite the fact that majority of urban pollutant aerosols consists of submicron size particles, systematic deposition data in this size range are virtually non-existent.

Traditionally, regional lung deposition has been assessed by inhalation of aerosols labeled with a γ -emitting radionuclide and subsequent lung scanning with a gamma camera over a period of 24 hours (8,9). This method is based on the premise that particles deposited in the ciliated airways are cleared out of the lung within 24 hours, so that the lung deposition can be obtained for two regions, the tracheobronchial (ciliated) and alveolar (non-ciliated) regions, by time-series measurements of particle activity in the lung. With head deposition data obtained from the initial scan, deposition values in the three respiratory compartments are determined. However, the method is laborious and cumbersome, involving radiolabelled aerosols and a long study time. Furthermore, recent studies of Gehr et al (10) have suggested that particle clearance from the ciliated airways may take much longer than 24 hours, complicating the premise of the clearance method. The scintigraphic lung scan image by a gamma camera provides a direct visual record of deposition distribution within the lung and a means of quantitative analysis for regional deposition to a certain extent (11-13). However, it is difficult to link the lung scan image to specific anatomic sites of the lung and the method remains largely qualitative. Because of lack of experimental data, mathematical and computer models have been used to estimate detailed regional lung deposition (14,15). However, these models are based on many assumptions on airway geometry and flow conditions, which do not represent the reality. Model predictions may not be warranted until they have been validated by experimental data.

2. Purpose

The purpose of this study is to investigate deposition dose of inhaled particles at local regions of the lung as well as in the whole lung and to compare the lung deposition characteristics between normal subjects and subjects with obstructive airway disease including cigarette smokers, asthmatics, and COPD patients. Effects of particle size (ultrafine, fine, and

coarse particles) and breathing pattern (slow vs fast and shallow vs deep) on lung deposition will be investigated in all of those subjects. Potential role of age and sex on lung deposition will also be investigated. Dose characteristics will be evaluated to identify susceptible populations and to elucidate potential mechanisms of PM health effects

3. Methods

Subject group: Five different groups of people including young normals (age = 18-40 years), old normals (age > 60 years), cigarette smokers (age = 18-40 years), asthmatics (age 18-40 years) and COPD patients will be recruited from the population in and around Chapel Hill, NC. Each group will consist of 20 people equal in number between male and female, totaling 100 subjects for all five groups. Two parallel studies will be performed, each study requiring the same number and composition in subject. Therefore, total of 200 subjects will be recruited. All potential subjects will undergo a screening procedure which includes the Minnesota Multiphasic Psychological Inventory (MMPI), complete medical history, physical examination, SMA-20 blood chemistry screen and a complete blood count (CBC) with differential. Black subjects will be screened for sickle cell disease; presence of sickle cell disease will result in exclusion from the study. Female subjects will be asked to provide a menstrual history and provide a urine specimen for pregnancy testing. Females believed to be pregnant will not be accepted into the study. To be included in this study, the subjects must also meet the following criteria:

A) Normal subject

1. No history of smoking within 5 year, and no history of more than 0.2 pack years prior to that.
2. No history of recreation drug use by inhalation within six months, and no history of recreational drug use by inhalation that regularly exceeded once per week prior to that.
3. No history of acute or chronic cardio-respiratory disease.
4. No personal history of hay fever or asthma.
5. No history compatible with acute respiratory infection of viral illness within the previous four weeks.
6. FVC > 80% of predicted normal value.
7. FEV₁ /FVC > 70% of predicted normal value.
8. Raw < 2 cm H₂O/l/s.

B) Cigarette Smokers

1. Current smokers who have been smoking cigarettes at least one pack a day for at least five years.
2. Same as normal criteria above from 2-8.

C) Asthmatics

1. FEV₁ /FVC > 60% of predicted normal value.
2. Same as normal criteria above from 1-5.

D) COPD subject

1. FEV₁ > 40% of predicted normal value.
2. FEV₁ /FVC > 40% of predicted normal value.

3. Same as normal criteria above from 2-5.

Accepted subjects will participate in a training session. Training session will consist of instructions in the performance of spirometry, body plethysmography, single-breath nitrogen washout test and the maintenance of consistent breathing pattern (flow rate and tidal volume) for the aerosol inhalation. Subjects may be excluded from further participation in the study on the basis of inadequate performance of the pulmonary function tests or the inability to maintain a controlled inhalation of aerosol.

Informed Consent: Informed consent will be obtained from the subjects after the purpose and procedures of the study and the potential risks from participation are explained. Each subject will then be asked to read a statement of informed consent. After ample opportunity to have any questions answered, the subject will sign the Informed Consent Form.

Subject recruitment: The test subjects will be recruited for this study by Bionetics Inc., under contract to the EPA. The majority of the subjects will be students and/or faculty-staff of the local universities. All subjects and potential subjects who have not completed the screening procedure and routine physical examination within the previous year will receive \$20.00 when they complete these. Subjects accepted into the protocol will be paid \$10.00 per hour during the testing period. In addition, a bonus of \$10.00 will be paid for arriving on time.

Pulmonary function test: Subjects' lung functions will be measured by a series of tests including body plethysmography, spirometry, and single-breath nitrogen washout test. In body plethysmography the subject will sit in a constant volume body box and perform a brief (~20 sec) panting maneuver against both an open and closed shutter for the measurement of airway resistance (R_{aw}) and thoracic gas volume (TGV). The specific airway resistance (sR_{aw}) will then be determined by the formula, $sR_{aw} = R_{aw} \times TGV$. In spirometry the subject will inhale to the maximum lung capacity and exhale rapidly and completely into a rolling seal spirometer. From this maneuver, the forced vital capacity (FVC), forced expiratory flow in one second (FEV1), maximal expiratory flows at 25, 50 and 75% of VC, peak expiratory flow rate, and the ratio FEV1/FVC will be measured. From a slow expiratory maneuver, the inspiratory capacity (IC), expiratory reserve volume (ERV), and vital capacity (VC) will be measured. The subject will then inhale a single breath of 100% oxygen and exhale all the way to the residual lung volume into a rolling seal spirometer. From the curve of nitrogen concentration vs expired volume the anatomic dead space will be determined according to the Fowler's method (16). The slope of phase III and closing volume will also be measured from the curve.

Test aerosols: Monodisperse test aerosols in the size range of 0.005 - 5 μm diameter will be generated by condensing oil vapor (di-2-ethylhexyl sebacate) on sodium chloride nuclei by means of evaporation-condensation techniques (model 3470, TSI Inc., St Paul, MN)(17). Particle concentration will be in the range of 10,000 - 80,000 particles/ cm^3 depending on particle size: the smaller the particle size, the greater the number concentration. Particle size will be measured by scanning mobility particle sizer (model 3934, TSI Inc.) for submicron particles and

by aerodynamic particle sizer (model 3310, TSI Inc.) with an aerosol diluter (model 3302, TSI Inc.) for particles $> 1 \mu\text{m}$ diameter. The sebacate oil ($\text{C}_{26}\text{H}_{50}\text{O}_4$, s.g. = 0.92 g/cm^3) is highly stable and nonhygroscopic and has been used in human inhalation studies for decades (18,19).

Experimental procedure: After a few practice breaths, the subject inhales filtered air via a laser aerosol photometer (25 ml dead space volume) from functional residual capacity (FRC) following a prescribed breathing pattern displayed on the computer screen. The subject then activates the data acquisition mode by pressing a hand-held switch during expiration followed by inhalation of a prescribed volume and exhales to residual volume (RV) at a constant flow rate. During the data acquisition mode, a small aerosol bolus ($\sim 45 \text{ ml}$ half width) will be introduced into the inspiratory stream by opening an aerosol valve for a predetermined duration of time. The duration of valve opening is adjusted between 50 - 250 ms depending on flow rate in order to maintain a consistent bolus volume; the faster the flow rate, the shorter the duration. The peak concentration of bolus is maintained at a level between 6 - 9 volts; the voltage level of 1 volt is equivalent to approximately $5000 \text{ particles/cm}^3$ for $1 \mu\text{m}$ diameter particles. The aerosol bolus is delivered to a lung depth (V_p) ranging from 100 - 500 ml with 50 ml increments. This procedure is repeated with monodisperse aerosols of three different particle sizes (1, 3 and $5 \mu\text{m}$ dia.) and for each particle size three different flow rates ($Q = 150, 250$ and 500 ml/s) will be used. In a parallel study deposition of three different submicron particles (0.06, 0.08, and $0.1 \mu\text{m}$) will be studied. In all tests the same flow rate will be used for both inspiration and expiration, and the inspiratory volume will be maintained at 500 ml from FRC. For a given bolus delivery condition at least five repeated measurements will be made. The aerosol bolus technique has been used successfully in previous studies (20,21).

In the same subject group lung deposition will be measured with non-bolus aerosols under the same inhalation conditions used for bolus aerosols. In addition to 500 ml tidal volume used for bolus study, breathing patterns of 1 liter tidal volume with varying flow rate (i.e., 250, 500, and 1000 l/sec) will also be used. Total deposition fraction (TDF) will be measured breath by breath with both single-breath maneuver (inhalation from FRC and exhalation to RV) and spontaneous continuous breathing maneuver (inhalation from FRC and exhalation to FRC) for one minute. Data will be collected for at least ten breaths for a given breathing condition. Lung deposition data with non-bolus aerosol will be used to compare with bolus deposition data and to ensure the accuracy of bolus method.

Experimental protocols: Each subject will have a medical history, personality profile, physical examination, and a blood screening test prior to selection as a subject. Selected subjects will be studied on three separate days, each day with one particle size. On the first day the subject will have a series of standard clinical tests to measure physiological lung functions after a brief training session (about one hour). If lung function test results meet the criteria of this study, the subject will be asked to inhale test aerosols in a prescribed manner and regional and total lung deposition will be measured. Regional deposition will be measured first with bolus aerosol method (about 3-4 hours) and total lung deposition will be measured with non-bolus aerosol (about 2 hours). Lung deposition measurement will be repeated with different size particles on second and third days.

Data collection and analysis: Respiratory flow rate, respiratory time, respiratory volume, and aerosol concentration will be monitored, collected, and processed on line with a dedicated personal computer (Dell 325) equipped with a high speed data acquisition board (DT2801A, Data Translation Inc.) and ASYST software (Keithly Instruments Inc.). Recovery of inhaled bolus aerosol will be obtained as a function of delivery depth of aerosol into the lung with varying inspiratory flow rate. Deposition dose in each of 50 ml volumetric lung regions as well as conventional three-compartment regions (i.e., upper, tracheobronchial, and alveolar regions) will be determined. Lung deposition will be calculated with respect to particle size and inhalation mode, and the results will be compared between normals and nonnormal subjects, between male and female, and between young and old subjects. The differences in deposition values among subject groups will be tested using an one-way analysis of variance, and all pairwise multiple comparisons between groups will be performed by Student Neuman-Keuls method. The difference between the groups will be considered to be significant if $p < 0.05$.

Risks to Subjects and Safeguards to Minimize Risks: Pulmonary function tests including spirometry, body plethysmography and single-breath N₂ washout test have little or no risk to the subject. During the initial physical exam, there is a possibility of a small hematoma or swelling developing at the site of blood sample collection.

Inhalation of bolus aerosols (di-2-ethylhexyl sebacate oil, DEHS) will have a minimal risk to the subject. DEHS oil will be used because 1) the aerosol has been used for inhalation studies in humans over a decade and there has been no report of adverse health effects (2,3,18-21) and 2) DEHS is highly stable at high temperature and suitable for generation of both small and large size particles by a condensation technique. DEHS is used as a plasticizer for elastomers and also used as a synthetic lubricant for jet engines. In France and Italy, DEHS is permitted for use in plastics that may come in contact with foodstuffs. There are a limited number of toxicological studies for DEHS but all of them show negative toxic effect (22).

Skin exposure studies conducted by Mallette et al (23) showed no irritation reactions in both animals and human subjects after the standard patch tests with 100% concentration of DEHS. A repeated tests for a period of two weeks did not show any signs of sensitization. An intraperitoneal injection of 6 gram/kg DEHS showed no signs of pathological changes after one month of observation in rats (23). The intraperitoneal and oral LD₅₀ values for rats and mouse was found between 12.8 and 25.6 g/kg of body weight, indicating a low level of oral and peritoneal toxicity (24). Swift et al. studied rats after a 4-hour exposure to 0.25-250 mg/m³ DEHS aerosol and they found no pulmonary and systemic effects (22). In this proposed study, the subject will inhale DEHS bolus aerosol (10 µg per bolus) about fifty breaths during a test day: therefore, total inhaled dose will be about 0.5 mg. However, because only a fraction of the inhaled particles (<10%) are expected to be deposited in the airways, the actual total lung dose will be < 50 µg. This dose is about 20 times below the dose tested in animals at which there was no harmful effect found.

Equipment and supplies

1. Condensation monodisperse aerosol generator: model 3470, TSI Inc. St. Paul MN
2. Monodisperse aerosol generator (MAGE): Laboro E Ambiente, Bologna, Italy
3. Aerodynamic particle sizer (APS): model 3310, TSI Inc.
4. Scanning mobility particle sizer (SMPS): model 3934, TSI Inc.
5. Aerosol diluter: model 3302, TSI Inc.
6. Laser aerosol inhalation system: custom made
7. Condensation particle counter (CPC): model 3022, TSI Inc.
8. Ultrafine condensation particle counter (UCPC): model 3025A, TSI Inc.
9. Gilibrator flow calibrator: Gilian Instruments Corp. NJ
10. Flow-volume monitor and computer interface: custom made
11. Three-way pneumatic sliding valve and control: model 4285, Hans Rudolf Inc., St. Louis
12. Personal computer: Dell 325 and Dell 310
13. Computer printer: Epson FX-850 and Epson LQ 870
14. Letec medical nebulizer: Letec Corp.
15. Latex particles: Duke Scientific Corp., Palo Alto, CA
16. Rotameters: Dwyer Instruments Inc., Michigan City, IN
17. Filtered air supplier: model 3074, TSI Inc.
18. Di-2-ethylhexyl sebacate oil: Sigma Chemical Inc., St. Louis, MO

Records

All pulmonary function data will be stored on-line in a centralized computer system which is managed by TRC Inc. under contract to EPA. The data will also be recorded manually on data sheet and subsequently inputted to PI's personal computer. The manual data sheet and floppy diskets of computer data files will be kept in PI's office during the study. Aerosol inhalation data will be collected on-line in a laboratory computer and stored in a hard disk driver of the computer. The raw data will then be zipped and copied to personal computers of PI and Co-PI. Backup tapes will also be made and kept in PI's office. PI and Co-PI will analyze and summarize the data, and the resulting data files will be kept in PI's office in the form of both floppy diskette and paper copy. All the data will be kept in PI's office until PI decides to transfer the files to a long-term storage.

Quality control requirements

Particle size of test aerosols will be measured by an aerodynamic particle sizer (APS) and a scanning mobility particle sizer (SMPS). The measurement accuracy of these instruments will be examined weekly by sampling latex particles with certified diameter. For APS two different size latex particles (i.e., 1.01, and 2.06 μm in diameter) will be used, whereas latex particles with 0.06 and 0.10 μm diameter will be used for calibrating SMPS. Measured particle size will be maintained within $\pm 5\%$ of the size of the certified latex particles.

Personnel assignments

Chong Kim (PI) of HSD will be responsible for overall design, progress, and outcome of the study including subject scheduling and screening, maintenance and calibration of experimental systems, and data management and storage. Dr. Kim will perform experiments to collect deposition data, analyze data, and write reports and manuscripts. Shu-Chieh Hu (Co-PI) of CEMLB/UNC will be responsible for system maintenance and daily experiments for coarse particle studies. Dr. Hu will analyze data and write reports and manuscripts. Dr. Jeffry Ding (post doctoral fellow) of CEMLB/UNC will perform experiments for submicron particle deposition studies. Dr. Ding will be responsible for routine maintenance of submicron aerosol inhalation system, data analysis and manuscript writing. Paulette DeWitt (technician) of HSD will assist Dr. Kim in collecting and analyzing pulmonary function data.

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- Page 1
1. **Date of Application:** September 1, 1991 (revised August, 1995, 1996)
2. **Title of Project:** Determination of Deposition Dose of Inhaled Particles in Human Lungs
3. **Principal Investigator:** Chong S. Kim, Ph.D.
Clinical Research Branch, U.S. EPA/
Department of Medicine
UNC-Chapel Hill
4. **Co-investigators:** Shu-Chieh Hu, Ph.D.
Center for Environmental Medicine and
Lung Biology, Department of Medicine,
UNC-Chapel Hill
- Andy Ghio, M.D.
Howard Kehrl, M.D.
Clinical Research Branch, U.S. EPA
5. **Granting Agency or Sponsor:** U.S. EPA and Center for Environmental
Medicine and Lung Biology, Department of
Medicine, UNC-Chapel Hill

6. Purpose and Rationale:

Purpose: The purpose of this study is to investigate deposition dose of inhaled particles at local regions of the lung as well as in the whole lung and to compare the lung deposition characteristics between normal subjects (young and old age group) and subjects with obstructive airway disease including cigarette smokers, asthmatics, and COPD patients. Effects of particle size (ultrafine, fine, and coarse particles) and breathing pattern (slow vs. fast and shallow vs. deep) on lung deposition will be investigated in all of those subjects. Potential role of age and sex on lung deposition will also be investigated. Dose characteristics will be evaluated to identify susceptible populations and to elucidate potential mechanisms of PM health effects.

Rationale: Deposition dose and site of inhaled particles within the lung are one of the key determinants in health risk assessment of particulate pollutants. Previous lung deposition studies have dealt largely with total lung deposition measurement, and a body of data has been reported for normal subjects with respect to particle size and the mode of inhalation (1-4). Those studies have shown that total lung deposition varies widely depending on particle size and breathing pattern: namely, the larger the particle size for particles $> 0.5 \mu\text{m}$ diameter or the smaller the particle size for particles $< 0.5 \mu\text{m}$ diameter, the greater the lung deposition. However, because particle deposition does not take place uniformly throughout the lung, there exist local regions of the lung at which deposition dose exceeds the average lung dose (5,6). It is also anticipated that local deposition varies to a much greater extent than total lung deposition, which may result in incidents of extreme dose enhancement at local regions. This may have significant implications in health risk assessment because a high local dose may cause tissue injuries and/or initiate a disease process (7), while the average lung dose is still in the acceptable

range. The information on detailed regional lung deposition is currently lacking. Furthermore, despite the fact that majority of urban pollutant aerosols consists of submicron size particles, systematic deposition data in this size range are virtually non-existent.

Traditionally, regional lung deposition has been assessed by inhalation of aerosols labeled with a γ -emitting radionuclide and subsequent lung scanning with a gamma camera over a period of 24 hours (8,9). This method is based on the premise that particles deposited in the ciliated airways are cleared out of the lung within 24 hours, so that the lung deposition can be obtained for two regions, the tracheobronchial (ciliated) and alveolar (non-ciliated) regions, by time-series measurements of particle activity in the lung. With head deposition data obtained from the initial scan, deposition values in the three respiratory compartments are determined. However, the method is laborious and cumbersome, involving radiolabelled aerosols and a long study time. Furthermore, recent studies of Gehr et al (10) have suggested that particle clearance from the ciliated airways may take much longer than 24 hours, complicating the premise of the clearance method. The scintigraphic lung scan image by a gamma camera provides a direct visual record of deposition distribution within the lung and a means of quantitative analysis for regional deposition to a certain extent (11-13). However, it is difficult to link the lung scan image to specific anatomic sites of the lung and the method remains largely qualitative. Because of lack of experimental data, mathematical and computer models have been used to estimate detailed regional lung deposition (14,15). However, these models are based on many assumptions on airway geometry and flow conditions, which do not represent the reality. Model predictions may not be warranted until they have been validated by experimental data.

7. Outline of the Study:

Pulmonary function test: Subjects's lung functions will be measured by a series of tests including body plethysmography, spirometry, and single-breath nitrogen washout test. In body plethysmography the subject will sit in a constant volume body box and perform a brief (~20 sec) panting maneuver against both an open and closed shutter for the measurement of airway resistance (R_{aw}) and thoracic gas volume (TGV). The specific airway resistance (sR_{aw}) will then be determined by the formula, $sR_{aw} = R_{aw} \times TGV$. In spirometry the subject will inhale to the maximum lung capacity and exhale rapidly and completely into a rolling seal spirometer. From this maneuver, the forced vital capacity (FVC), forced expiratory flow in one second (FEV1), maximal expiratory flows at 25, 50 and 75% of VC, peak expiratory flow rate, and the ratio FEV1/FVC will be measured. From a slow expiratory maneuver, the inspiratory capacity (IC), expiratory reserve volume (ERV), and vital capacity (VC) will be measured. The subject will then inhale a single breath of 100% oxygen and exhale all the way to the residual lung volume into a rolling seal spirometer. From the curve of nitrogen concentration vs. expired volume the anatomic dead space will be determined according to the Fowler's method (16). The slope of phase III and closing volume will also be measured from the curve.

Test aerosols: Monodisperse test aerosols in the size range of 0.004 -5 μm diameter will be generated by condensing oil vapor (di-2-ethylhexyl sebacate) on sodium chloride nuclei by means of evaporation-condensation techniques (model 3470, TSI Inc., St Paul, MN) (17). Particle concentration will be in the range of 10,000 -80,000 particles/ cm^3 depending on particles size: the smaller the particle size, the greater the number concentration. Particle size will be measured by scanning mobility particle sizer (model 3934, TSI Inc.) for submicron particles and by aerodynamic particle sizer (model 3310, TSI Inc.) with an aerosol diluter (model 3302, TSI

Inc.) for particles $> 1 \mu\text{m}$ diameter. The sebacate oil ($\text{C}_{26}\text{H}_{50}\text{O}_4$, s.g. = 0.92 g/cm^3) is highly stable and nonhygroscopic and has been used in human inhalation studies for decades (18,19).

Experimental procedure: After a few practice breaths, the subject inhales filtered air via a laser aerosol photometer (25 ml dead space volume) from functional residual capacity (FRC) following a prescribed breathing pattern displayed on the computer screen. The subject then activates the data acquisition mode by pressing a hand-held switch during expiration followed by inhalation of a prescribed volume and exhales to residual volume (RV) at a constant flow rate. During the data acquisition mode, a small aerosol bolus ($\sim 45 \text{ ml}$ half width) will be introduced into the inspiratory stream by opening an aerosol valve for a predetermined duration of time. The duration of valve opening is adjusted between 50 - 250 ms depending on flow rate in order to maintain a consistent bolus volume; the faster the flow rate, the shorter the duration. The peak concentration of bolus is maintained at a level between 6 - 9 volts; the voltage level of 1 volt is equivalent to approximately $5000 \text{ particles/cm}^3$ for $1 \mu\text{m}$ diameter particles. The aerosol bolus is delivered to a lung depth (V_p) ranging from 100 - 500 ml with 50 ml increments. This procedure is repeated with monodisperse aerosols of three different particle sizes (1, 3 and $5 \mu\text{m}$ in diameter) and for each particle size three different flow rates ($Q = 150, 250$ and 500 ml/s) will be used (study name, ADEPOSIT). In a parallel study deposition of four different submicron particles (0.04, 0.06, 0.08, and $0.1 \mu\text{m}$ in diameter) will be studied (study name, SDEPOSIT). Experimental procedures are identical between ADEPOSIT and SDEPOSIT except for particle size. In all tests the same flow rate will be used for both inspiration and expiration, and the inspiratory volume will be maintained at 500 ml from FRC. For a given bolus delivery condition at least five repeated measurements will be made. The aerosol bolus technique has been used successfully in previous studies (20,21).

In the same subject group lung deposition will be measured with non-bolus aerosols under the same inhalation conditions used for bolus aerosols. In addition to 500 ml tidal volume used for bolus study, breathing patterns of 1 liter tidal volume with varying flow rate (e.g., 250, 500, and 1000 ml/sec) will also be used. Total deposition fraction (TDF) will be measured breath by breath with both single-breath maneuver (inhalation from FRC and exhalation to RV) and spontaneous continuous breathing maneuver (inhalation from FRC and exhalation to FRC) for one minute. Data will be collected for at least ten breaths for a given breathing condition. Lung deposition data with non-bolus aerosol will be used to compare with bolus deposition data and to ensure the accuracy of bolus method.

Experimental protocols: Each subject will have a medical history, personality profile, physical examination, and a blood screening test prior to selection as a subject. Selected subjects will be studied on three separate days, each day with one particle size. On the first day the subject will have a series of standard clinical tests to measure physiological lung functions after a brief training session (about one hour). If results of the lung function test meet the criteria of this study, the subject will be asked to inhale test aerosols in a prescribed manner and regional and total lung deposition will be measured. Regional deposition will be measured first with bolus aerosol method (about 3-4 hours) and total lung deposition will be measured with non-bolus aerosol (about 2 hours). Lung deposition measurement will be repeated with different size particles on second and third or fourth days: ADEPOSIT for 1, 3, and $5 \mu\text{m}$ diameter particles and SDEPOSIT for 0.04, 0.06, 0.08, and $0.1 \mu\text{m}$ diameter particles. ADEPOSIT and SDEPOSIT will be conducted in parallel and independently, and the same subjects will be encouraged to participate in both studies.

Data collection and analysis: Respiratory flow rate, respiratory time, respiratory volume, and aerosol concentration will be monitored, collected, and processed on line with a dedicated personal computer (Dell 325) equipped with a high speed data acquisition board (DT2801A, Data Translation Inc.) and ASYST software (Keithly Instruments Inc.). Recovery of inhaled bolus aerosol will be obtained as a function of delivery depth of aerosol into the lung with varying inspiratory flow rate. Deposition dose in each of 50 ml volumetric lung regions as well as conventional three-compartment regions (i.e., upper, tracheobronchial, and alveolar regions) will be determined. Lung deposition will be calculated with respect to particle size and inhalation mode, and the results will be compared between normals and non-normal subjects, between male and female, and between young and old subjects. The differences in deposition values among subject groups will be tested using an one-way analysis of variance, and all pairwise multiple comparisons between groups will be performed by Student Neuman-Keuls method. The difference between the groups will be considered to be significant if $p < 0.05$.

8. Duration of Study and Duration of Subject's Participation:

The study will begin in the Fall of 1991 and will take about a year per one subject group. Completion of two parallel studies will take approximately 7-8 years. Each subject is required to make three or four separate visits to our laboratory and each visit will require about four-seven hours of time.

9. Subjects:

Five different groups of people including young normals (age = 18-40 years), old normals (age > 60 years), cigarette smokers (age = 18-40 years), asthmatics (age 18-40 years) and COPD patients (age > 40 years) will be recruited from the population in and around Chapel Hill, NC. Each group will consist of 20 people equal in number between male and female, totaling 100 subjects for all five groups. Two parallel studies will be performed, each study requiring the same number and composition in subject. Therefore, total of 200 subjects will be recruited. All potential subjects will undergo a screening procedure which includes the Minnesota Multiphasic Psychological Inventory (MMPI), complete medical history, physical examination, SMA-20 blood chemistry screen and a complete blood count (CBC) with differential. Black subjects will be screened for sickle cell disease; presence of sickle cell disease will result in exclusion from the study. Female subjects will be asked to provide a menstrual history and provide a urine specimen for pregnancy testing. Females believed to be pregnant will not be accepted into the study. To be included in this study, the subjects must also meet the following criteria:

A) Normal subject (age = 18-40 years)

1. No history of smoking within 5 year, and no history of more than 0.2 pack years prior to that.
2. No history of recreation drug use by inhalation within six months, and no history of recreational drug use by inhalation that regularly exceeded once per week prior to that.
3. No cardiac or renal disease, or no insulin dependent diabetes.
4. No personal history of hay fever or asthma.
5. No acute respiratory infection of viral illness within the previous four weeks.
6. $FVC > 80\%$ of predicted normal value.
7. $FEV_1 / FVC > 70\%$ of predicted normal value.
8. $Raw < 2 \text{ cm H}_2\text{O/l/s}$.

B) Elderly subjects (age > 60 years)

1. $FEV_1 / FVC > 60\%$ of predicted normal value.
2. Same as normal criteria above except for 7

C) Cigarette Smokers (age = 18-40 years)

1. Current smokers who have been smoking cigarettes at least one pack a day for at least five years.
2. Same as normal criteria above from 2-8.

D) Asthmatics (age = 18-40 years)

1. $FEV_1 / FVC > 60\%$ of predicted normal value.
2. Same as normal criteria above from 1-5.

E) COPD subject (age > 40 years)

1. $FEV_1 > 40\%$ of predicted normal value.
2. $FEV_1 / FVC > 40\%$ of predicted normal value.
3. Same as normal criteria above from 2-5.
4. Non-smokers are preferred, but current smokers also are accepted.

Accepted subjects will participate in a training session. Training session will consist of instructions in the performance of spirometry, body plethysmography, single-breath nitrogen washout test and the maintenance of consistent breathing pattern (flow rate and tidal volume) for the aerosol inhalation. Subjects may be excluded from further participation in the study on the basis of inadequate performance of the pulmonary function tests or the inability to maintain a controlled inhalation of aerosol

10. Anticipated Benefits to Subjects and/or Society:

Subjects will receive a complete medical examination free of charge and the results of the exam will be accessible to the subjects. Subjects will receive a payment for participating in the study.

11. Risks to Subjects and Safeguards to Minimize Risks:

Pulmonary function tests including spirometry, body plethysmography and single-breath N₂ washout test have little or no risk to the subject. During the initial physical exam, there is a possibility of a small hematoma or swelling developing at the site of blood sample collection.

Inhalation of bolus aerosols (di-2-ethylhexyl sebacate oil, DEHS) will have a minimal risk to the subject. DEHS oil will be used because 1) the aerosol has been used for inhalation studies in humans over a decade and there has been no report of adverse health effects (2,3,18-21) and 2) DEHS is highly stable at high temperature and suitable for generation of both small and large size particles by a condensation technique. DEHS is used as a plasticizer for elastomers and also used as a synthetic lubricant for jet engines. In France and Italy, DEHS is permitted for use in plastics that may come in contact with foodstuffs. There are a limited number of toxicological studies for DEHS but all of them show negative toxic effect (22).

Skin exposure studies conducted by Mallette et al (23) showed no irritation reactions in both animals and human subjects after the standard patch tests with 100% concentration of DEHS. A repeated tests for a period of two weeks did not show any signs of sensitization. An intraperitoneal injection of 6 gram/kg DEHS showed no signs of pathological changes after one month of observation in rats (23). The intraperitoneal and oral LD50 values for rats and mouse was found between 12.8 and 25.6 g/kg of body weight, indicating a low level of oral and peritoneal toxicity (24). Swift et al. studied rats after a 4-hour exposure to 0.25-250 mg/m³

DEHS aerosol and they found no pulmonary and systemic effects (22). In this proposed study, the subject will inhale DEHS bolus aerosol (10 µg per bolus) about fifty breaths during a test day; therefore, total inhaled dose will be about 0.5 mg. However, because only a fraction of the inhaled particles (<10%) are expected to be deposited in the airways, the actual total lung dose will be < 50 µg. This dose is about 20 times below the dose tested in animals at which there was no harmful effect found.

12. Informed Consent:

Informed consent will be obtained from the subjects after the purpose and procedures of the study and the potential risks from participation are explained. Each subject will then be asked to read a statement of informed consent. After ample opportunity to have any questions answered, the subject will sign the Informed Consent Form.

13. Costs to be Borne by Subjects: None

14. Use of Radioactive Materials: None

15. Statement of Agreements:

The Principal Investigator, whose signature appears below agrees to a continuing exchange of information or advice with the committee on the Protection of the Rights of Human subjects.

The Principal Investigator agrees to communicate with the Committee to obtain its approval before institution of any significant change or addition to the project or before continuing beyond the expiration date.

The Principal Investigator agrees to inform the Committee and Hospital Risk Management upon the occurrence of any previously unsuspected or serious adverse effects or complications.

The Principal Investigator agrees to provide each subject with a copy of the signed consent form and to keep the original of the signed consent form in the subject's file.

Signature of P.I.

Summary

Project Title: Determination of Deposition Dose of Inhaled Particles in Human Lungs
Principal Investigator: Chong S. Kim, Ph. D., USEPA/NHEERL (Telephone: 966-5049)

Study Name: ADEPOSIT (fine and coarse particle study)
SDEPOSIT (ultrafine particle study)

Procedure: After completion of your lung function test, you will have a brief training on inhalation method to be used, which consists basically of three different breathing rates (slow, normal, and fast breathing) with a fixed volume of air. You will be asked to inhale via a mouthpiece a single breath of clean air containing a pulse of aerosol with one of these breathing patterns and exhale all the way to empty the lung. This breathing maneuver will be repeated approximately two hundred times. After completion of this test, you will inhale the same aerosol from a large bag with a wide range of breathing patterns varying from shallow and fast to deep and slow breathing (simulating a variety of breathing patterns that you may have during daily activities, i.e., sleep, seating, walking, exercise, etc.) for a total of approximately 150 breaths, about 10 breaths per each different breathing pattern. The breathing patterns that you will follow may not be identical to your natural breathing pattern and you may need a conscious effort to follow the patterns. You will be asked to visit the EPA facility 3 times each on different days. The study on each day will take about 6-8 hours (including break times and lunch hour) depending on your ability to follow the prescribed breathing patterns.

Subjects: 1) young adult (age < 40 years)
2) elderly (age > 60 years)
3) heavy smokers (age < 40 years)
4) asthmatics (age < 40 years)
5) patients with COPD (age > 40 years)

Subject number: N=20 (10 males and 10 females) for each of the five groups

Study Protocol:

Prior to participation of this study: screening tests
Medical history, personality profile, physical exam, and blood screening

During study:

1) Normal subjects: *full protocol*

Day 1: Initial training (~1 hour) followed by inhalation of first test aerosols, about 6-7 hours

Day 2: inhalation of second test aerosol (bolus and non-bolus), about 6 hours

Day 3: same as Day 2, but with third test aerosol.

2) Elderly (conditional) and Patients with COPD: *abbreviated protocol*

Day 1: lung function test and initial training of inhalation protocol followed by inhalation of first test aerosol, about four-five hours

Day 2: inhalation of second test aerosol, about four hours

Day 3: same as Day 2, but with third test aerosol.

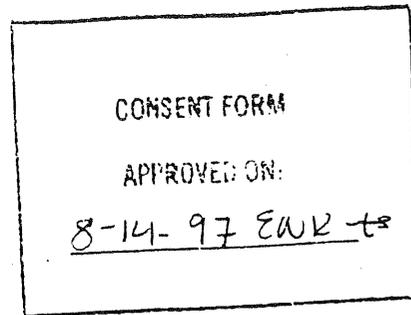
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UNC Hospitals
Chapel Hill, North Carolina

UNC-CH Study # 91-EPA-226



CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Determination of Deposition Dose of Inhaled Particles in Human Lungs

Principal Investigator: Chong S. Kim, Ph.D.
Phone number: 919-966-5049

Co-investigator: Shu-Chieh Hu, Ph.D.
Phone number: 919-966-6227

You are asked to take part in a research study under the direction of Chong S. Kim, Ph.D. and the medical supervision of Elston Seal, M.D. Other professional persons who work with them may assist or act for them. You will be one of approximately 160 subjects in this research study.

Purpose:

The purpose of this research study is to investigate how much of inhaled particles deposit in different regions of the lung and how the lung deposition changes with the size of aerosol particles you are inhaling and the pattern of breathing.

Duration:

Your participation in this study will require three visits each on separate days within two weeks. On each day of visit the study will last for approximately six hours.

Procedures:

During the course of this study, the following will occur:

1. You will have a medical history, personality profile, standard physical examination, and a blood screening test administered to you prior to your selection as a subject.
2. On your first visit to the laboratory, you will have a series of standard clinical tests to measure physiological functions of your lung after a brief training session (about one hour). If your lung function test results meet the criteria of this study, you will be enrolled for this study.
3. After completion of your lung function test, you will be asked to inhale a test aerosol through a mouthpiece in three prescribed breathing patterns (slow, normal,

and fast breathing) displayed on a computer monitor screen. The breathing patterns that you will follow will not be much different from your ordinary breathing pattern. You will breathe a few breaths at a time and during breathing a small pulse of aerosol will be injected into the inspiratory air stream of a selected breath. This breathing maneuver will be repeated approximately two hundred times. After completion of this test, you will inhale the same test aerosol from a large bag continuously for approximately fifty breaths. The whole test will take about 6 hours.

4. On your second visit, after standard lung function tests you will inhale second test aerosol in the same manner as the first visit. The whole test will take about 6 hours.
5. On your third visit, you will inhale third test aerosol. The inhalation procedures will be the same as the ones on the first and second visit. The whole test will take about 6 hours.

Exclusions:

You should not participate in this study if any of the following apply to you:

1. You are allergic to dust or oil mist.
2. You are female and pregnant, or you have any reason to believe that you are pregnant.
3. You have experienced acute respiratory infection of viral illness within the previous four weeks.
4. You have used recreation drug or narcotics by inhalation within the previous four weeks.

Risks and Discomforts:

This study might involve the following risks and/or discomforts to you:

Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect your health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect your health.

The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil aerosol may have a minimal risk to your health. The amount of DEHS oil that you will inhale on each test day is about 50 μg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. If you are an asthmatic or a person with chronic bronchitis, the lung dose of inhaled aerosol may be substantially greater than the values given above depending on the severity of your abnormal lung conditions. The oil aerosol has been used for inhalation studies in both normals and persons with obstructive lung disease for a decade and no adverse health effects have been reported.

When you are required to have a bronchial challenge test, the inhalation of methacholine or histamine aerosols will cause a mild bronchial constriction. This may cause a feeling of "tightness" within your chest. This feeling should disappear in about 30 minutes. However, in any events that you feel uncomfortable and want to be treated, you will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. You may also feel a slight throat irritation which may make you cough. The irritation is transient and usually disappears in about 15 min. With histamine aerosols, you may notice flushing, rapid heart beat, lightheadedness (dizziness), or mild headache, all

of which are transient.

Some risks are unforeseeable in participating in this study.

Benefits:

The benefits to you of participating in this study may be: A complete medical examination free of charge. You will also receive a payment for participating in the study. New data obtained from this study may help us understand how pollutant particles in the air affect our health and develop a means of better protecting our health from pollutant particles in the air.

New Findings:

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

Confidentiality:

Every effort will be taken to protect the identity of the participants in this study. However, there is no guarantee that the information cannot be obtained by legal process or court order. No subjects will be identified in any report or publication of this study or its results.

Financial costs of the research:

The costs of this research will be paid by research fund provided by The U.S. Environmental Protection Agency.

Compensation in case of injury:

In the event of personal injury resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by The University of North Carolina at Chapel Hill. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment but The University of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). You do not waive any liability rights for personal injury by signing this form.

Payments to Participants:

You will receive \$10.00 per hour for your participation in this study. In addition, you will receive \$10.00 as a bonus for arriving promptly at the appointed time. You will also receive \$20.00 when you complete the initial screening and physical examination if you have not had them within the previous year. In the event that your participation is terminated before completion of the study, you will receive a payment for the time you will actually have participated.

Right to refuse or to withdraw from the study:

Your participation is voluntary. You may refuse to participate, or may discontinue your participation at any time without penalty, or jeopardizing your continuing medical care at this institution, or losing benefits you would otherwise be entitled to.

Dr. Chong Kim has the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Offer to Answer Questions:

You have the opportunity to ask, and to have answered, all your questions about this research. If you have other questions, or if a research-related injury occurs, you may call Chong Kim, Ph.D. at 919-966-5049.

Institutional Review Board Approval:

This project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If you believe that there is any infringement upon my rights, you may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Subject's Agreement:

I have read the information provided above. I voluntarily agree to participate in this study. After it is signed I understand I will receive a copy of this consent form.

Signature of Research Subject

Date

Signature of Person Obtaining Consent

Date

UNC Hospitals
Chapel Hill, North Carolina

UNC-CH Study # 91-EPA-226

CONSENT FORM

PROCESSED ON:

2-18-98 ENK-1c

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Determination of Deposition Dose of Inhaled Particles in Human Lungs

Principal Investigator: Chong S. Kim, Ph.D. (919-966-5049)
Co-investigator: Shu-Chieh Hu, Ph.D. (919-966-6227)
Co-investigator: Peter Jaques, Ph.D. (919-966-6216)
Co-investigator: Howard Kehrl, M.D. (919-966-6208)
Co-investigator: Andy Ghio, M.D. (919-966-0670)

You are asked to take part in a research study under the direction of Chong S. Kim, Ph.D. and the medical supervision of Elston Seal, M.D. Other professional persons who work with them may assist or act for them. You will be one of approximately 160 subjects in this research study.

Purpose:

The purpose of this research study is to investigate how much of inhaled particles deposit in different regions of the lung and how the lung deposition changes with the size of aerosol particles you are inhaling and the pattern of breathing.

Duration:

Your participation in this study will require three visits each on separate days within two weeks. On each day of visit the study will last for approximately six hours. If you are an individual with chronic obstructive pulmonary disease, the study time will be approximately four hours in each visit.

Procedures:

During the course of this study, the following will occur:

1. You will have a medical history, personality profile, standard physical examination, and a blood screening test administered to you prior to your selection as a subject.
2. On your first visit to the laboratory, you will have a series of standard clinical tests to measure physiological functions of your lung. If your lung function test results meet the criteria of this study, you will be enrolled for this study.

3. After completion of your lung function test, you will be asked to inhale a small pulse of test aerosol through a mouthpiece in three prescribed breathing patterns (slow, normal, and fast breathing) displayed on a computer monitor screen. You will inhale a single breath of clean air containing a pulse of aerosol and exhale all the way to empty the lung. This breathing maneuver will be repeated approximately two hundred times. After completion of this test, you will inhale the same aerosol from a large bag with a wide range of breathing patterns varying from shallow and fast to deep and slow breathing for a total of approximately 150 breaths, about 10 breaths per each different breathing pattern. The breathing patterns that you will follow will be somewhat different than your ordinary breathing patterns, and you may need a conscious effort to follow the patterns. The whole test including the initial training for the breathing maneuver will take about 6-8 hours including break times and lunch hour.
4. On your second visit, after standard lung function tests you will inhale second test aerosol in the same manner as the first visit. The whole test will take about 6 hours.
5. On your third visit, you will inhale third test aerosol. The inhalation procedures will be the same as the ones on the first and second visit. The entire test will take about 6 hours. However, the study time may vary depending on your ability to follow the prescribed breathing patterns.
6. Occasionally you may be asked if you want to make additional visits in order to repeat the whole or some parts of the above procedures. However, you have no obligation to accept the request.
7. If you are an individual with chronic obstructive airway disease, the above procedures will be trimmed down and the study time will be reduced to approximately four hours in each visit. After completion of the daily study, you will have a clinical lung function test before you are discharged.

Exclusions:

You should not participate in this study if any of the following apply to you:

1. You are allergic to dust or oil mist.
2. You are female and pregnant, or you have any reason to believe that you are pregnant.
3. You have experienced acute respiratory infection or viral illness within the previous four weeks.
4. You have used recreation drug or narcotics by inhalation within the previous four weeks.
5. You have a cardiac or kidney disease, or diabetes requiring an insulin therapy.

Risks and Discomforts:

This study might involve the following risks and/or discomforts to you:

Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect your health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect your health.

The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil aerosol may have a minimal risk to your health. The amount of DEHS oil that you will inhale on each test day is about 50 μg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. If you are an asthmatic or a person with chronic bronchitis, the lung dose of inhaled aerosol may be substantially greater than the values given above depending on the severity of your abnormal lung conditions. The oil aerosol has been used for inhalation studies in both healthy individuals and persons with obstructive lung disease for a decade and no adverse health effects have been reported.

Some risks are unforeseeable in participating in this study.

Benefits:

The benefits to you of participating in this study may be: A complete medical examination free of charge. You will also receive a payment for participating in the study. New data obtained from this study may help us understand how pollutant particles in the air affect our health and develop a means of better protecting our health from pollutant particles in the air.

New Findings:

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

Confidentiality:

Every effort will be taken to protect the identity of the participants in this study. However, there is no guarantee that the information cannot be obtained by legal process or court order. No subjects will be identified in any report or publication of this study or its results.

Financial costs of the research:

The costs of this research will be paid by research fund provided by The U.S. Environmental Protection Agency.

Compensation in case of injury:

In the event of personal injury resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by The University of North Carolina at Chapel Hill. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment but The University of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). You do not waive any liability rights for personal injury by signing this form.

Payments to Participants:

You will receive \$10.00 per hour for your participation in this study. In addition, you will receive \$10.00 as a bonus for arriving promptly at the appointed time on each study day and \$20.00 as a completion bonus when you complete the three-day study. You will also receive \$20.00 when you complete the initial screening and physical examination if

you have not had them within the previous year. In the event that your participation is terminated before completion of the study, you will receive a payment for the time you will actually have participated .

Right to refuse or to withdraw from the study:

Your participation is voluntary. You may refuse to participate, or may discontinue your participation at any time without penalty, or jeopardizing your continuing medical care at this institution, or losing benefits you would otherwise be entitled to.

Dr. Chong Kim has the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Offer to Answer Questions:

You have the opportunity to ask, and to have answered, all your questions about this research. If you have other questions, or if a research-related injury occurs, you may call Chong Kim, Ph.D. at 919-966-5049 or Howard Kehrl, M.D. at 919-966-6208 or Andy Ghio, M.D. at 919-966-0670.

Institutional Review Board Approval:

This project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If you believe that there is any infringement upon my rights, you may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Subject's Agreement:

I have read the information provided above. I voluntarily agree to participate in this study. After it is signed I understand I will receive a copy of this consent form.

Signature of Research Subject

Date

Signature of Person Obtaining Consent

Date

UNC Hospitals
Chapel Hill, North Carolina

UNC-CH Study # 91-EPA-226

CONSENT FORM
APPROVED ON:
<u>7/28/95 ENK-mb</u>

A DEPOSIT
S DEPOSIT

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Determination of Deposition Dose of Inhaled Particles in Human Lungs

Principal Investigator: Chong S. Kim, Ph.D.
Phone Number: 919-966-5049

Co-investigator: Shu-Chieh Hu, Ph.D.
Peter Jaques, Ph.D.
Howard Kehrl, M.D.
Andy Ghio, M.D.

You are asked to take part in a research study under the direction of Chong S. Kim, Ph.D. and the medical supervision of Elston Seal, M.D. Other professional persons who work with them may assist or act for them. You will be one of approximately 160 subjects in this research study.

Purpose:

The purpose of this research study is to investigate how much of inhaled particles deposit in different regions of the lung and how the lung deposition changes with the size of aerosol particles you are inhaling and the pattern of breathing.

Duration:

Your participation in this study will require three visits each on separate days within two weeks. On each day of visit the study will last for approximately six hours. If you are an individual with chronic obstructive pulmonary disease, the study time will be approximately four hours in each visit.

Procedures:

During the course of this study, the following will occur:

1. You will have a medical history, personality profile, standard physical examination, and a blood screening test administered to you prior to your selection as a subject.
2. On your first visit to the laboratory, you will have a series of standard clinical tests to measure physiological functions of your lung. If your lung function test results meet the criteria of this study, you will be enrolled for this study.
3. After completion of your lung function test, you will be asked to inhale a small pulse of test aerosol through a mouthpiece in three prescribed breathing patterns (slow, normal, and fast)

breathing) displayed on a computer monitor screen. You will inhale a single breath of clear air containing a pulse of aerosol and exhale all the way to empty the lung. This breathing maneuver will be repeated approximately two hundred times. After completion of this test, you will inhale the same aerosol from a large bag with a wide range of breathing patterns varying from shallow and fast to deep and slow breathing for a total of approximately 150 breaths, about 10 breaths per each different breathing pattern. The breathing patterns that you will follow will be somewhat different than your ordinary breathing patterns, and you may need a conscious effort to follow the patterns. The whole test including the initial training for the breathing maneuver will take about 6-8 hours including break times and lunch hour.

4. On your second visit, after standard lung function tests you will inhale second test aerosol in the same manner as the first visit. The whole test will take about 6 hours.
5. On your third visit, you will inhale third test aerosol. The inhalation procedures will be the same as the ones on the first and second visit. The entire test will take about 6 hours. However, the study time may vary depending on your ability to follow the prescribed breathing patterns.
6. Occasionally you may be asked if you want to make additional visits in order to repeat the whole or some parts of the above procedures. However, you have no obligation to accept the request.
7. If you are an individual with chronic obstructive airway disease, the above procedures will be trimmed down and the study time will be reduced to approximately four hours in each visit. After completion of the daily study, you will have a clinical lung function test before you are discharged.

Exclusions:

You should not participate in this study if any of the following apply to you:

1. You are allergic to dust or oil mist.
2. You are female and pregnant, or you have any reason to believe that you are pregnant.
3. You have experienced acute respiratory infection of viral illness within the previous four weeks.
4. You have used recreation drug or narcotics by inhalation within the previous four weeks.
5. You have a cardiac or kidney disease, or diabetes requiring an insulin therapy.

Risks and Discomforts:

This study might involve the following risks and/or discomforts to you:

Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect your health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect your health.

The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil aerosol may have a minimal risk to your health. The amount of DEHS oil that you will inhale on each test day is about 50 µg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. If you are an asthmatic or a person with chronic bronchitis, the lung dose of inhaled aerosol may be substantially greater than the values given above depending on the severity of your abnormal lung conditions. The oil aerosol has been used for inhalation studies in both healthy individuals and

A/S - Deposit

CONSENT

APPROVED

7-13-99 ENK/mb

UNC ~~Hospitals~~
Chapel Hill, North Carolina

UNC-CH Study # 91-EPA-226

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Determination of Deposition Dose of Inhaled Particles in Human Lungs

Principal Investigator: Chong S. Kim, Ph.D.
Phone Number: 919-966-5049

Co-investigator: Shu-Chieh Hu, Ph.D.
Peter Jaques, Ph.D.
Howard Kehrl, M.D.
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Purpose:

The purpose of this research study is to investigate how much of inhaled particles deposit in different regions of the lung and how the lung deposition changes with the size of aerosol particles you are inhaling and the pattern of breathing.

Duration:

Your participation in this study will require three visits each on separate days within two weeks. On each day of visit the study will last for approximately six hours. If you are an individual with chronic obstructive pulmonary disease, the study time will be approximately four hours in each visit.

Procedures:

During the course of this study, the following will occur:

1. You will have a medical history, personality profile, standard physical examination, and a blood screening test administered to you prior to your selection as a subject.
2. On your first visit to the laboratory, you will have a series of standard clinical tests to measure physiological functions of your lung. If your lung function test results meet the criteria of this study, you will be enrolled for this study.
3. After completion of your lung function test, you will be asked to inhale a small pulse of test aerosol through a mouthpiece in three prescribed breathing patterns (slow, normal, and fast

breathing) displayed on a computer monitor screen. You will inhale a single breath of clean air containing a pulse of aerosol and exhale all the way to empty the lung. This breathing maneuver will be repeated approximately two hundred times. After completion of this test, you will inhale the same aerosol from a large bag with a wide range of breathing patterns varying from shallow and fast to deep and slow breathing for a total of approximately 150 breaths, about 10 breaths per each different breathing pattern. The breathing patterns that you will follow will be somewhat different than your ordinary breathing patterns, and you may need a conscious effort to follow the patterns. The whole test including the initial training for the breathing maneuver will take about 6-8 hours including break times and lunch hour.

4. On your second visit, after standard lung function tests you will inhale second test aerosol in the same manner as the first visit. The whole test will take about 6 hours.
5. On your third visit, you will inhale third test aerosol. The inhalation procedures will be the same as the ones on the first and second visit. The entire test will take about 6 hours. However, the study time may vary depending on your ability to follow the prescribed breathing patterns.
6. Occasionally you may be asked if you want to make additional visits in order to repeat the whole or some parts of the above procedures. However, you have no obligation to accept the request.
7. If you are an individual with chronic obstructive airway disease, the above procedures will be trimmed down and the study time will be reduced to approximately four hours in each visit. After completion of the daily study, you will have a clinical lung function test before you are discharged.

Exclusions:

You should not participate in this study if any of the following apply to you:

1. You are allergic to dust or oil mist.
2. You are female and pregnant, or you have any reason to believe that you are pregnant.
3. You have experienced acute respiratory infection of viral illness within the previous four weeks.
4. You have used recreation drug or narcotics by inhalation within the previous four weeks.
5. You have a cardiac or kidney disease, or diabetes requiring an insulin therapy.

Risks and Discomforts:

This study might involve the following risks and/or discomforts to you:

Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect your health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect your health.

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persons with obstructive lung disease for a decade and no adverse health effects have been reported.

Some risks are unforeseeable in participating in this study.

Benefits:

The benefits to you of participating in this study may be: A complete medical examination free of charge. You will also receive a payment for participating in the study. New data obtained from this study may help us understand how pollutant particles in the air affect our health and develop a means of better protecting our health from pollutant particles in the air.

New Findings:

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

Confidentiality:

Every effort will be taken to protect the identity of the participants in this study. However, there is no guarantee that the information cannot be obtained by legal process or court order. No subjects will be identified in any report or publication of this study or its results.

Financial costs of the research:

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Compensation in case of injury:

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Payments to Participants:

You will receive \$10.00 per hour for your participation in this study. In addition, you will receive \$10.00 as a bonus for arriving promptly at the appointed time on each study day and \$50.00 as a completion bonus when you complete the three-day study. You will also receive \$20.00 when you complete the initial screening and physical examination if you have not had them within the previous year. In the event that your participation is terminated before completion of the study, you will receive a payment for the time you will actually have participated.

Right to refuse or to withdraw from the study:

Your participation is voluntary. You may refuse to participate, or may discontinue your participation at any time without penalty, or jeopardizing your continuing medical care at this institution, or losing benefits you would otherwise be entitled to.

Dr. Chong Kim has the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Offer to Answer Questions:

You have the opportunity to ask, and to have answered, all your questions about this research. If you have other questions, or if a research-related injury occurs, you may call Chong Kim, Ph.D. at 919-966-5049 or Howard Kehrl, M.D. at 919-966-6208 or Andy Ghio, M.D. at 919-966-0670.

Institutional Review Board Approval:

This project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If you believe that there is any infringement upon my rights, you may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Subject's Agreement:

I have read the information provided above. I voluntarily agree to participate in this study. After it is signed I understand I will receive a copy of this consent form.

Signature of Research Subject

Date

Signature of Person Obtaining Consent

Date

UNC Hospitals
Chapel Hill, North Carolina

UNC-CH Study # 91-EPA-226

6-27-00 6-27-01
13

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Determination of Deposition Dose of Inhaled Particles in Human Lungs

Principal Investigator: Chong S. Kim, Ph.D.
Phone Number: 919-966-5049

Co-investigator: Shu-Chieh Hu, Ph.D.
Howard Kehrl, M.D.
Andy Ghio, M.D.

You are asked to take part in a research study under the direction of Chong S. Kim, Ph.D. and the medical supervision of Elston Seal, M.D. Other professional persons who work with them may assist or act for them. You will be one of approximately 160 subjects in this research study.

Purpose:

The purpose of this research study is to investigate how much of inhaled particles deposit in different regions of the lung and how the lung deposition changes with the size of aerosol particles you are inhaling and the pattern of breathing.

Duration:

Your participation in this study will require three visits each on separate days within two weeks. On each day of visit the study will last for approximately six hours. If you are an individual with chronic obstructive pulmonary disease, the study time will be approximately four hours in each visit.

Procedures:

During the course of this study, the following will occur:

1. You will have a medical history, personality profile, standard physical examination, and a blood screening test administered to you prior to your selection as a subject.
2. On your first visit to the laboratory, you will have a series of standard clinical tests to measure physiological functions of your lung. If your lung function test results meet the criteria of this study, you will be enrolled for this study.
3. After completion of your lung function test, you will be asked to inhale a small pulse of test aerosol through a mouthpiece in three prescribed breathing patterns (slow, normal, and fast breathing) displayed on a computer monitor screen (**bolus aerosol protocol**). You will inhale a single breath of clean air containing a pulse of aerosol and exhale all the way to empty the lung. This breathing maneuver will be repeated approximately two

2. I will have an initial training session which involves instruction in the performance of breathing maneuvers necessary to test the physiological function of my lung.
3. Following training, I will be asked to perform breathing tests before and after inhaling methacholin or histamine aerosol which causes a slight bronchial narrowing. I will also inhale, in a prescribed manner, a number of (about one hundred) breaths of sebacete oil aerosol.
4. I will make two visits to the laboratory at least a week apart to participate in the study. During each visit, total time for training and actual testing will be approximately 5 hours.

B. I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.
2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to my health. The amount of DEHS oil that I will inhale on each test day is about 50 μ g that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.
3. The inhalation of methacholine and histamine aerosols will cause a mild bronchial constricton. This may cause a feeling of "tightness" within my lung. This feeling should disappear in about 30 minutes. However, in any events that I feel uncomfortable and want to be treated, I will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. With histamine aerosols, I may also notice flushing, rapid heart beat, lightheadedness, or mild headache, all of which are transient.
4. I understand that some risks are unforeseeable in participating in this study.

C. I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in the study.

UNC Hospitals
Chapel Hill, North Carolina

Study Number: 91-EPA-226

CONSENT FORM

APPROVED ON:

1-8-92

JCH-1c

INFORMED CONSENT FORM

Determination of Deposition Dose of Inhaled Particles
in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D.
(966-5049)
Coinvestigators: Shu-Chieh Hu, Ph.D.
(966-6239)
Timothy Gerrity, Ph.D.
(966-6206)
Howard Kehrl, M.D.
(966-6207)

The purpose of this research is to investigate how much of inhaled particles deposit in the bronchial airways and how the airway deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

- A. I understand that the following is a brief description of the research and of my participation in it:
1. I will have a medical history, personality profile, physical examination, and a blood screening test administered to me prior to my selection as a subject.

the study.

2. I may terminate my participation in the study at any time for any reason I wish without prejudice.
3. The investigator may terminate my participation in the study at any time.
4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.
5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, John C. Herion, M.D., (919) 966-1344.

Signature of Volunteer: _____

Witness: _____ Date: _____

administered to me prior to my selection as a subject.

2. I will have an initial training session which involves instruction in the performance of breathing maneuvers necessary to test the physiological function of my lung.
3. Following training, I will be asked to perform breathing tests which consist of breathing air in and out of various medical devices in a prescribed manner. I will also inhale, in a prescribed manner, a number of (about one hundred) breaths of sebacete oil aerosol.
4. I will make two visits to the laboratory at least a week apart to participate in the study. During each visit, total time for training and actual testing will be approximately 5 hours.

B. I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.
2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to my health. The amount of DEHS oil that I will inhale on each test day is about 50 μ g that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.
3. The inhalation of methacholine and histamine aerosols will cause a mild bronchial constricton. This may cause a feeling of "tightness" within my lung. This feeling should disappear in about 30 minutes. However, in any events that I feel uncomfortable and want to be treated, I will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. With histamine aerosols, I may also notice flushing, rapid heart beat, lightheadedness, or mild headache, all of which are transient.
4. I understand that some risks are unforeseeable in participating in this study.

C. I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in

UNC Hospitals
Chapel Hill, North Carolina

Study Number:

CONSENT FORM

APPROVED ON:

10-25-91 JCH-1c

INFORMED CONSENT FORM

**Determination of Deposition Dose of Inhaled Particles
in Human Lung Airways**

Principal Investigator: Chong S. Kim, Ph.D.
(966-5049)

Coinvestigators: Shu-Chieh Hu, Ph.D.
(966-6239)

Timothy Gerrity, Ph.D.
(966-6206)

Howard Kehrl, M.D.
(966-6207)

The purpose of this research is to investigate how much of inhaled particles deposit in the bronchial airways and how the airway deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours the file cabinet, and the room in which the file cabinet is kept are locked. During non-working hours, Medical Research Building C itself is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

A. I understand that the following is a brief description of the research and of my participation in it:

1. I will have a medical history, personality profile, physical examination, and a blood screening test

federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). You do not waive any liability rights for personal injury by signing this form.

What if you want to stop before your part in the study is complete?

You can withdraw from this study at any time, without penalty. Dr. Chong Kim has the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instruction, or because the entire study has been stopped.

What if you have questions about this study?

You have the right to ask, and to have answered, any you may have about this research. If you have further questions, or if a research-related injury occurs, you may call Chong Kim, Ph.D. at 919-966-5049 or Howard Kehrl, M.D. at 919-966-6208 or Elston Seal, M.D. at 919-966-6217.

What if you have questions about your rights as a subjects?

This project has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects (Medical IRB) at the University of North Carolina at Chapel Hill. If you have any questions or concerns regarding your rights as a research subject, you may contact the Chairman of the Committee at (919) 966-1344.

Subject's Agreement:

I have read the information provided above. I voluntarily agree to participate in this study.

Signature of Research Subject

Date

Printed Name of Research Subject

Signature of Person Obtaining Consent

Date

Printed Name of Person Obtaining Consent

What are the possible benefits?

The benefits to you of participating in this study may be: a complete medical examination free of charge. New data obtained from this study may help us understand how pollutant particles in the air affect our health and develop a means of better protecting our health from pollutant particles in the air.

What if we learn about new risks during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

How will your privacy be protected?

No subject will be identified in any report or publication about this study. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-CH will take all steps allowable by law to protect the privacy of personal information. You will be identified by a number assigned to you and all personal files are stored in a cabinet placed in a locked room which is accessible only by investigators.

Will you be paid for participating?

You will receive \$12.00 per hour for your participation in this study. In addition, you will receive \$12.00 as a bonus for arriving promptly at the appointed time on each study day and \$50.00 as a completion bonus when you complete the three-day study. You will also receive \$20.00 when you complete the initial screening and physical examination if you have not had them within the previous year. In the event that your participation is terminated before completion of the study, you will receive a payment for the time you will actually have participated.

Will it cost you anything to participate?

The costs of this research will be paid by research fund provided by the U.S. Environmental Protection Agency. There will be no costs to you for participating.

Who is sponsoring this research?

This research is funded by the U.S. Environmental Protection Agency. This means that the research team is being compensated by the sponsor for conducting the study. The researchers do not, however, hold a direct financial interest in the sponsor or in the product being studied.

What will happen if you are injured by this research?

This study involves only minimal risk that are not greater, considering both probability and magnitude, than those encountered in daily life or during the performance of routine physical examinations. In the event of personal injury resulting from the research procedures, financial compensation cannot be provided by the University of North Carolina at Chapel Hill. However, in the event that a physical injury is proximately caused by the negligence of a

6. Occasionally, you may be asked if you want to make additional visits in order to repeat the whole or some parts of the above procedures. However, you have no obligation to accept the request.
7. If you are an individual with chronic obstructive airway disease, or you are an elderly person with an age of 60 years or greater, the above procedures will be trimmed down and the study time will be reduced to approximately four hours in each visit. After completion of the daily study, you will have a clinical lung function test before you are discharged.
8. If you are participating in a subset of this study requiring only **normal aerosol protocol**, you will make two visits, each on separate days. In each visit, you will inhale several different test aerosols with predetermined breathing patterns. Study time will be approximately six hours for each visit.

Are there any reasons you should not participate?

You should not participate in this study if any of the following apply to you:

1. You are allergic to dust or oil mist.
2. You are female and pregnant, or you have any reason to believe that you are pregnant.
3. You have experienced acute respiratory infection of viral illness within the previous four weeks.
4. You have used recreation drug or narcotics by inhalation within the previous four weeks.
5. You have a cardiac or kidney disease, or diabetes requiring an insulin therapy.

What are the possible risks or discomfort?

This study might involve the following risks and/or discomforts to you:

Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect your health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect your health.

The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil aerosol may have a minimal risk to your health. The amount of DEHS oil that you will inhale on each test day is about 50 µg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. If you are an asthmatic or a person with chronic bronchitis, the lung dose of inhaled aerosol may be substantially greater than the values given above depending on the severity of your abnormal lung conditions. The oil aerosol has been used for inhalation studies in both healthy individuals and persons with obstructive lung disease for a decade and no adverse health effects have been reported. Salt aerosols (NaCl, common table salt) used in a subset of this study do not have any harmful effects.

In addition, there may be uncommon or previously unrecognized risks that might occur.

What is the purpose of this study?

The purpose of this research study is to investigate how much of inhaled fine particles deposit in your lung and how the lung deposition changes with the size of aerosol particles you are inhaling and with the ways that you inhale, fast or slow and deep and shallow.

How many subjects will participate in this study?

If you decide to participate, you will be one of approximately 220 subjects in this research study.

How long will your participation last?

Your participation in this study will require three visits, each on separate days within two weeks. On each day of visit the study will last for approximately six hours. If you are an individual with chronic obstructive pulmonary disease, the study time will be approximately four hours in each visit.

What will happen if you take part in the study?

During the course of this study, the following will occur:

1. You will have a medical history, personality profile, standard physical examination, and a blood screening test administered to you prior to your selection as a subject.
2. On your first visit to the laboratory, you will have a series of standard clinical tests to measure physiological functions of your lung. If your lung function test results meet the criteria of this study, you will be enrolled for this study.
3. After completion of your lung function test, you will be asked to inhale a small pulse of test aerosol through a mouthpiece in three prescribed breathing patterns (slow, normal, and fast breathing) displayed on a computer monitor screen (**bolus aerosol protocol**). You will inhale one breath of clean air containing a pulse of aerosol and exhale all the way to empty the lung. This breathing maneuver will be repeated approximately two hundred times. After completion of this test, you will inhale the same aerosol from a large collapsible bag with a variety of breathing patterns that you may use in your actual daily activity. Ten to fifteen different breathing patterns may be attempted and you will breath about 10 breaths for each different breathing pattern (**normal aerosol protocol**). The breathing patterns that you will follow will be somewhat different than your natural breathing patterns, and you may need a conscious effort to follow the patterns. The whole test including the initial training for the breathing maneuver will take about 6-8 hours including break times and lunch hour.
4. On your second visit, after standard lung function tests you will inhale second test aerosol in the same manner as the first visit. The whole test will take about 6 hours.
5. On your third visit, you will inhale third test aerosol. The inhalation procedures will be the same as the ones on the first and second visit. The entire test will take about 6 hours. However, the study time may vary depending on your ability to follow the prescribed breathing patterns.

University of North Carolina-Chapel Hill
Consent to Participate in a Research Study
Adult Subjects

This consent form should be signed only
between 6/26/01 and 6/26/02

Approved by School of Medicine IRB

Medical IRB # _____

Consent Form Version Date: _____

Title of Study: Determination of Deposition Dose of Inhaled Particles in Human Lungs

Principal Investigator: Chong S. Kim, Ph.D.
UNC-CH Department: Department of Medicine
Phone Number: 919-966-5049

Co-investigator: Howard Kehrl, M.D.

Sponsor: U.S. Environmental Protection Agency

You are being asked to take part in a research study. The investigators listed above are in charge of the study under the medical supervision of Elston Seal, M.D. Other professional persons may also help or act for them.

What are some general things you should know about research studies?

Research studies are designed to gain scientific knowledge that may help other people in the future. You may not receive direct benefit from participating. There may also be risks associated with participating in research studies.

Your participation is voluntary. you may refuse to participate, or may withdraw your consent to participate in any study at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your doctor. If you are a patient with an illness, you do not have to participate in research in order to receive treatment.

Details about this particular study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators name above, or staff members who may assist them, any questions you have about this study at any time.

Dr. Chong Kim has the right to stop your participation in the study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Offer to Answer Questions:

You have the opportunity to ask, and to have answered, all your questions about this research. If you have other questions, or if a research-related injury occurs, you may call Chong Kim, Ph.D. at 919-966-5049 or Howard Kehrl, M.D. at 919-966-6208 or Andy Ghio, M.D. at 919-966-0670.

Institutional Review Board Approval:

This project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If you believe that there is any infringement upon my rights, you may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Subject's Agreement:

I have read the information provided above. I voluntarily agree to participate in this study. After it is signed I understand I will receive a copy of this consent form.

Signature of Research Subject

Date

Signature of Person Obtaining Consent

Date

be substantially greater than the values given above depending on the severity of your abnormal lung conditions. The oil aerosol has been used for inhalation studies in both healthy individuals and persons with obstructive lung disease for a decade and no adverse health effects have been reported. Salt aerosols (NaCl) used in a subset of this study do not have any harmful effects.

Some risks are unforeseeable in participating in this study.

Benefits:

The benefits to you of participating in this study may be: A complete medical examination free of charge. You will also receive a payment for participating in the study. New data obtained from this study may help us understand how pollutant particles in the air affect our health and develop a means of better protecting our health from pollutant particles in the air.

New Findings:

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

Confidentiality:

Every effort will be taken to protect the identity of the participants in this study. However, there is no guarantee that the information cannot be obtained by legal process or court order. No subjects will be identified in any report or publication of this study or its results.

Financial costs of the research:

The costs of this research will be paid by research fund provided by The U.S. Environmental Protection Agency.

Compensation in case of injury:

In the event of personal injury resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by The University of North Carolina at Chapel Hill. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the researchers will assist you in obtaining appropriate medical treatment but The University of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). You do not waive any liability rights for personal injury by signing this form.

Payments to Participants:

You will receive \$12.00 per hour for your participation in this study. In addition, you will receive \$12.00 as a bonus for arriving promptly at the appointed time on each study day and \$50.00 as a completion bonus when you complete the three-day study. You will also receive \$20.00 when you complete the initial screening and physical examination if you have not had them within the previous year. In the event that your participation is terminated before completion of the study, you will receive a payment for the time you will actually have participated.

Right to refuse or to withdraw from the study:

Your participation is voluntary. You may refuse to participate, or may discontinue your participation at any time without penalty, or jeopardizing your continuing medical care at this institution, or losing benefits you would otherwise be entitled to.

hundred times. After completion of this test, you will inhale the same aerosol from a large bag with a wide range of breathing patterns varying from shallow and fast to deep and slow breathing for a total of approximately 150 breaths, about 10 breaths per each different breathing pattern (**normal aerosol protocol**). The breathing patterns that you will follow will be somewhat different than your ordinary breathing patterns, and you may need a conscious effort to follow the patterns. The whole test including the initial training for the breathing maneuver will take about 6-8 hours including break times and lunch hour.

4. On your second visit, after standard lung function tests you will inhale second test aerosol in the same manner as the first visit. The whole test will take about 6 hours.
5. On your third visit, you will inhale third test aerosol. The inhalation procedures will be the same as the ones on the first and second visit. The entire test will take about 6 hours. However, the study time may vary depending on your ability to follow the prescribed breathing patterns.
6. Occasionally, you may be asked if you want to make additional visits in order to repeat the whole or some parts of the above procedures. However, you have no obligation to accept the request.
7. If you are an individual with chronic obstructive airway disease, the above procedures will be trimmed down and the study time will be reduced to approximately four hours in each visit. After completion of the daily study, you will have a clinical lung function test before you are discharged.
8. If you are participating in a subset of this study requiring only **normal aerosol protocol**, you will make two visits each on separate days. In each visit, you will inhale several different test aerosols with predetermined breathing patterns. Study time will be about six hours during each visit.

Exclusions:

You should not participate in this study if any of the following apply to you:

1. You are allergic to dust or oil mist.
2. You are female and pregnant, or you have any reason to believe that you are pregnant.
3. You have experienced acute respiratory infection of viral illness within the previous four weeks.
4. You have used recreation drug or narcotics by inhalation within the previous four weeks.
5. You have a cardiac or kidney disease, or diabetes requiring an insulin therapy.

Risks and Discomforts:

This study might involve the following risks and/or discomforts to you:

Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect your health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect your health.

The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil aerosol may have a minimal risk to your health. The amount of DEHS oil that you will inhale on each test day is about 50 µg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. If you are an asthmatic or a person with chronic bronchitis, the lung dose of inhaled aerosol may

2. I may terminate my participation in the study at any time for any reason I wish without prejudice.
3. The investigator may terminate my participation in the study at any time.
4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.
5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, John C. Herion, M.D., (919) 966-1344.

Signature of Volunteer: _____

Witness: _____ Date: _____

UNC Hospitals
Chapel Hill, North Carolina

Study Number: 91. EPA-226

2-5-92 JCH-1c

INFORMED CONSENT FORM

**Determination of Deposition Dose of Inhaled Particles
in Human Lung Airways**

Principal Investigator: Chong S. Kim, Ph.D.
(966-5049)
Coinvestigators: Shu-Chieh Hu, Ph.D.
(966-6239)
Timothy Gerrity, Ph.D.
(966-6206)
Howard Kehrl, M.D.
(966-6207)

The purpose of this research is to investigate how much of inhaled particles deposit in the bronchial airways and how the airway deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

A. I understand that the following is a brief description of the research and of my participation in it:

1. I will have a medical history, personality profile, physical examination, and a blood screening test administered to me prior to my selection as a subject.

2. On my first visit to the laboratory (about 2 hour time), I will have an initial training session which involves instruction in the performance of breathing maneuvers necessary to test the physiological function of my lung.
3. On my second visit, after lung function tests I will inhale, in a prescribed manner, a number of (about one hundred) breaths of sebacate oil aerosol. The study will take about 6 hours.
4. On my third and fourth visits (about 3 hours each), I will be asked to perform breathing tests before and after inhaling methacholine or histamine aerosol which causes a slight bronchial narrowing. I will also inhale about 30 breaths of sebacate aerosol on each visit. The two visits will be separated at least a week apart.

B. I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.
2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to my health. The amount of DEHS oil that I will inhale on each test day is about 50 μ g that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.
3. The inhalation of methacholine and histamine aerosols will cause a mild bronchial constriction. This may cause a feeling of "tightness" within my lung. This feeling should disappear in about 30 minutes. However, in any events that I feel uncomfortable and want to be treated, I will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. With histamine aerosols, I may also notice flushing, rapid heart beat, lightheadedness, or mild headache, all of which are transient.
4. I understand that some risks are unforeseeable in participating in this study.

C. I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in

the study.

2. I may terminate my participation in the study at any time for any reason I wish without prejudice.
3. The investigator may terminate my participation in the study at any time.
4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.
5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, John C. Herion, M.D., (919) 966-1344.

Signature of Volunteer: _____

Witness: _____ Date: _____

UNC Hospitals
Chapel Hill, North Carolina

Study Number:

CONSENT FORM

APPROVED ON:

9-3-92 ENK-1c

INFORMED CONSENT FORM

- Determination of Deposition Dose of Inhaled Particles
in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D.
(966-5049)
Coinvestigators: Shu-Chieh Hu, Ph.D.
(966-6239)
Timothy Gerrity, Ph.D.
(966-6206)
Howard Kehrl, M.D.
(966-6207)

The purpose of this research is to investigate how much of inhaled particles deposit in the bronchial airways and how the airway deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

A. I understand that the following is a brief description of the research and of my participation in it:

1. I will have a medical history, personality profile, physical examination, and a blood screening test administered to me prior to my selection as a subject.

2. On my first visit to the laboratory (about 2 hour time), I will have an initial training session which involves instruction in the performance of breathing maneuvers necessary to test the physiological function of my lung.
3. On my second visit, after lung function tests I will inhale, in a prescribed manner, a number of (about one hundred) breaths of sebacate oil aerosol. The study will take about 6 hours.
4. On my third and fourth visits (about 3 hours each), I will be asked to perform breathing tests before and after inhaling methacholine or histamine aerosol which causes a slight bronchial narrowing. I will also inhale about 30 breaths of sebacate aerosol on each visit. The two visits will be separated at least a week apart.

B. I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.
2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to my health. The amount of DEHS oil that I will inhale on each test day is about 50 μ g that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.
3. The inhalation of methacholine and histamine aerosols will cause a mild bronchial constriction. This may cause a feeling of "tightness" within my lung. This feeling should disappear in about 30 minutes. However, in any events that I feel uncomfortable and want to be treated, I will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. With histamine aerosols, I may also notice flushing, rapid heart beat, lightheadedness, or mild headache, all of which are transient.
4. I understand that some risks are unforeseeable in participating in this study.

C. I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in

the study.

2. I may terminate my participation in the study at any time for any reason I wish without prejudice.
3. The investigator may terminate my participation in the study at any time.
4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.
5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Signature of Volunteer: _____

Signature of Investigator: _____ Date: _____

UNC Hospitals
Chapel Hill, North Carolina

Study Number: 91-EPA-226

CONSENT FORM

APPROVED ON:

9-2-93 ENK-1c

INFORMED CONSENT FORM

Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D.
(966-5049)

Coinvestigators: Shu-Chieh Hu, Ph.D.
(966-6239)

Timothy Gerrity, Ph.D.
(966-6206)

Howard Kehrl, M.D.
(966-6207)

The purpose of this research is to investigate how much of inhaled particles deposit in the bronchial airways and how the airway deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

A. I understand that the following is a brief description of the research and of my participation in it:

1. I will have a medical history, personality profile, physical examination, and a blood screening test administered to me prior to my selection as a subject.

2. On my first visit to the laboratory (about 2 hour time), I will have an initial training session which involves instruction in the performance of breathing maneuvers necessary to test the physiological function of my lung.

3. On my second visit, after lung function tests I will inhale, in a prescribed manner, a number of (about one hundred) breaths of sebacate oil aerosol. The study will take about 6 hours.

4. On my third and fourth visits (about 3 hours each), I will be asked to perform breathing tests before and after inhaling methacholine or histamine aerosol which causes a slight bronchial narrowing. I will also inhale about 30 breaths of sebacate aerosol on each visit. The two visits will be separated at least a week apart.

B. I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.

2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to my health. The amount of DEHS oil that I will inhale on each test day is about 50 μg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.

3. The inhalation of methacholine and histamine aerosols will cause a mild bronchial constriction. This may cause a feeling of "tightness" within my lung. This feeling should disappear in about 30 minutes. However, in any events that I feel uncomfortable and want to be treated, I will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. I may also feel a slight throat irritation which may make me cough. The irritation is transient and usually disappears in about 15 min. With histamine aerosols, I may notice flushing, rapid heart beat, lightheadedness (dizziness), or mild headache, all of which are transient.

4. I understand that some risks are unforeseeable in participating in this study.

C. I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality.

If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in the study.

2. I may terminate my participation in the study at any time for any reason I wish without prejudice.
3. The investigator may terminate my participation in the study at any time.
4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.
5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Signature of Volunteer: _____

Witness: _____ Date: _____

UNC Hospitals
Chapel Hill, North Carolina

Study Number: 91-EPA-226

CONSENT FORM
APPROVED ON:
11-15-93 ENK/wfm

INFORMED CONSENT FORM

Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D. (966-5049)
Coinvestigators: Shu-Chieh Hu, Ph.D. (966-6239)
Timothy Gerrity, Ph.D. (966-6206)

The purpose of this research is to investigate how much of inhaled particles deposit in the bronchial airways and how the airway deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

- A). I understand that the following is a brief description of the research and of my participation in it:
1. I will have a medical history, personality profile, physical examination, and a blood screening test administered to me prior to my selection as a subject.
 2. On my first visit to the laboratory (about 2 hour time), I will have an initial

training session which involves instruction in the performance of breathing maneuvers necessary to test the physiological function of my lung.

3. On my second visit, after lung function tests I will inhale, in a prescribed manner, a number of (about one hundred) breaths of sebacate oil aerosol. The study will take about 6 hours.
4. On my third and fourth visits (about 3 hours each), I will be asked to perform breathing tests before and after inhaling methacholine or histamine aerosol which causes a slight bronchial narrowing. I will also inhale about 30 breaths of sebacate aerosol on each visit. The two visits will be separated at least a week apart.

B). I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.
2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to my health. The amount of DEHS oil that I will inhale on each test day is about 50 μg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.
3. The inhalation of methacholine and histamine aerosols will cause a mild bronchial constriction. This may cause a feeling of "tightness" within my lung. This feeling should disappear in about 30 minutes. However, in any events that I feel uncomfortable and want to be treated, I will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. I may also feel a slight throat irritation which may make me cough. The irritation is transient and usually disappears in about 15 min. With histamine aerosols, I may notice flushing, rapid heart beat, lightheadedness (dizziness), or mild headache, all of which are transient. I understand that both methacholine and histamine are not FDA approved drugs, but they have been used clinically for decades. Only agents with high quality (purity \geq 98%) will be used in this study.
4. I understand that some risks are unforeseeable in participating in this study.

C). I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in

strict confidentiality. If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in the study.

2. I may terminate my participation in the study at any time for any reason I wish without prejudice.
3. The investigator may terminate my participation in the study at any time.
4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.
5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Signature of Volunteer: _____

Witness: _____ Date: _____

CONSENT FORM

UNC Hospitals
Chapel Hill, North Carolina

6-24-94 ENK-1c

Study Number: _____

INFORMED CONSENT FORM

Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D. (966-5049)
Coinvestigators: Shu-Chieh Hu, Ph.D. (966-6239)
Timothy Gerrity, Ph.D. (966-6206)

The purpose of this research is to investigate how much of inhaled particles deposit in the bronchial airways and how the airway deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

- A). I understand that the following is a brief description of the research and of my participation in it:
1. I will have a medical history, personality profile, physical examination, and a blood screening test administered to me prior to my selection as a subject.

2. On my first visit to the laboratory (about 2 hour time), I will have an initial training session which involves instruction in the performance of breathing maneuvers necessary to test the physiological function of my lung.

3. On my second visit, after lung function tests I will inhale, in a prescribed manner, a number of (about one hundred) breaths of sebacate oil aerosol. The study will take about 6 hours.

B). I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.

2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to my health. The amount of DEHS oil that I will inhale on each test day is about 50 μg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.

3. I understand that some risks are unforeseeable in participating in this study.

C). I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in the study.

2. I may terminate my participation in the study at any time for any reason I wish without prejudice.

3. The investigator may terminate my participation in the study at any time.

4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.

5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this

study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Signature of Volunteer: _____

Witness: _____ Date: _____

JNC Hospitals
Chapel Hill, North Carolina

Study Number: 91EPA-226

CONSENT FORM

APPROVED ON:

8-30-94 ENK-1c

INFORMED CONSENT FORM

Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D. (966-5049)
Coinvestigators: Shu-Chieh Hu, Ph.D. (966-6239)
Howard Kehrl, M.D. (966-6208)

The purpose of this research is to investigate how much of inhaled particles deposit in the bronchial airways and how the airway deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

A). I understand that the following is a brief description of the research and of my participation in it:

1. I will have a medical history, personality profile, physical examination, and a blood screening test administered to me prior to my selection as a subject.

2. On my first visit to the laboratory, I will have a series of standard clinical tests to measure physiological functions of my lung after a brief training session (about one hour). If my lung function test results meet the criteria of this study, I will inhale test aerosols in a prescribed manner (about 3 hours).
3. On my second visit, after lung function tests I will inhale, in a prescribed manner (same as the first visit), about two hundred breaths of test aerosols. The study will take about 4 hours.
4. On my third visit, I will inhale test aerosols in the same manner as the second visit. The study will take about 4 hours.

B). I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.
2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to my health. The amount of DEHS oil that I will inhale on each test day is about 50 μg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.
3. I understand that some risks are unforeseeable in participating in this study.

C). I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in the study.
2. I may terminate my participation in the study at any time for any reason I wish without prejudice.
3. The investigator may terminate my participation in the study at any time.
4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.

5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Signature of Volunteer: _____

Witness: _____ Date: _____

UNC Hospitals
Chapel Hill, North Carolina

Study Number: 91-EPA-226

CONSENT FORM

APPROVED ON:

2-2-95 ENK-1c

INFORMED CONSENT FORM

Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D. (966-5049)
Co-investigators: Shu-Chieh Hu, Ph.D. (966-6239)
Howard Kehrl, M.D. (966-6208)

The purpose of this research is to investigate how much of inhaled particles deposit in the lung and how the lung deposition changes with breathing patterns.

I have had the purpose, procedures, and possible risks of this study explained to me before agreeing to participate. I have been given an opportunity to ask any questions about the procedures or about any other aspects of this research. I understand that the study itself will have no direct benefit to me and that I may withdraw at any time without prejudice and without loss of pay for the time I have already invested in the study.

I have been assured that all data will be collected according to an identification code number and that I will not be identified by name in any report or publication of this study or its results. All of my medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. I understand that every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order.

A). I understand that the following is a brief description of the research and of my participation in it:

1. I will have a medical history, personality profile, physical examination, and a blood screening test administered to me prior to my selection as a subject.

2. On my first visit to the laboratory, I will have a series of standard clinical tests to measure physiological functions of my lung after a brief training session (about one hour). If my lung function test results meet the criteria of this study, I will inhale test aerosols in a prescribed manner (about 3 hours).
3. On my second visit, after lung function tests I will inhale, in a prescribed manner (same as the first visit), about two hundred breaths of test aerosols. The study will take about 4 hours.
4. On my third visit, I will inhale test aerosols in the same manner as the second visit. The study will take about 4 hours.

B). I understand the following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect my health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect my health.
2. The inhalation of di-(2-ethylhexyl) sebacate oil may have a minimal risk to my health. The amount of the oil that I will inhale on each test day is about $50 \mu\text{g}$ that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. If I am an asthmatic or of chronic bronchitis, the lung dose of inhaled aerosol may be substantially greater than the values given above depending on the severity of my abnormal lung conditions. The oil compound has been used for inhalation studies in both normals and patients with obstructive lung disease for a decade and no adverse health effects have been reported.
3. When I am required to have a bronchial challenge test, the inhalation of methacholine or histamine aerosols will cause a mild bronchial constriction. This may cause a feeling of "tightness" within my lung. This feeling should disappear in about 30 minutes. However, in any events that I feel uncomfortable and want to be treated, I will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. I may also feel a slight throat irritation which may make me cough. The irritation is transient and usually disappears in about 15 min. With histamine aerosols, I may notice flushing, rapid heart beat, lightheadedness (dizziness), or mild headache, all of which are transient.
4. I understand that some risks are unforeseeable in participating in this study.

C). I also understand that:

1. If I am female, I will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in

strict confidentiality. If I am pregnant or have any reason to believe that I may be pregnant, I may not participate in the study.

2. I may terminate my participation in the study at any time for any reason I wish without prejudice.
3. The investigator may terminate my participation in the study at any time.
4. I will be paid \$10.00 per hour for my participation in this study. In addition, I will receive \$10.00 as a bonus for arriving promptly at the appointed time. I will also receive \$20.00 when I complete the initial screening and physical examination if I have not had them within the previous year. I will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.
5. The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Howard Kehrl, M.D. (919) 966-6208.

I have been informed that a licensed physician will be on call in the facility at all times.

I understand that in the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, I might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). I understand that I do not waive any liability rights for personal injury by signing this form.

I understand that this project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If I believe that there is any infringement upon my rights, I may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

Signature of Volunteer: _____

Witness: _____ Date: _____

UNC Hospitals
Chapel Hill, North Carolina

UNC-CH Study # 91-EPA-226

<p>CONSENT FORM</p> <p>APPROVED ON:</p> <p><u>8-8-95</u> <u>ENK-1c</u></p>
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CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D. (966-5049)
Coinvestigator: Shu-Chieh Hu, Ph.D. (966-6227)
Howard Kehrl, M.D. (966-6208)

You are asked to participate in a research study whose purpose is to investigate how much of inhaled particles deposit in the bronchial airways and how the lung deposition changes with the size of aerosol particles you are inhaling and the pattern of breathing. You will be one of approximately 150 subjects in this research study.

- A). Your participation in this study will require three visits on separate days and during the course of this study, the following will occur:
1. You will have a medical history, personality profile, physical examination, and a blood screening test administered to you prior to your selection as a subject.
 2. On your first visit to the laboratory, you will have a series of standard clinical tests to measure physiological functions of your lung after a brief training session (about one hour). If your lung function test results meet the criteria of this study, you will be asked to inhale test aerosols in a prescribed manner (about 6 hours).
 3. On your second visit, after lung function tests you will inhale, in a prescribed manner (same as the first visit), about two hundred breaths of test aerosols. The study will take about 6 hours.
 4. On your third visit, you will inhale test aerosols in the same manner as the second visit. The study will take about 6 hours.

B). The following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect your health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect your health.
2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to your health. The amount of DEHS oil that you will inhale on each test day is about 50 μg that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. This compound has been used in human inhalation studies for a decade and no adverse health effects have been reported.
3. Some risks are unforeseeable in participating in this study.

C). Exclusions and Termination:

1. If you are female, you will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If you are pregnant or have any reason to believe that you may be pregnant, you may not participate in the study.
2. Your participation is voluntary. You may refuse to participate, or discontinue your participation at any time without penalty, or losing benefits you would otherwise be entitled to.
3. The investigator has the right to terminate your participation in the study at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or the entire study has been stopped.

D) Confidentiality:

All of your medical and personal records will be maintained in a file cabinet in the Nurses' Station of Medical Research Building C. During non-working hours, Medical Research Building C is locked and attended by a guard. Every effort will be taken to protect the identity of the participants in this study. However, there is no guaranty that the information cannot be obtained by legal process or court order. No subjects will be identified by name in any report or publication of this study or its results.

E) Benefits:

You will be paid \$10.00 per hour for your participation in this study. In addition, you will receive \$10.00 as a bonus for arriving promptly at the appointed time. You will also receive \$20.00 when you complete the initial screening and physical examination if you have not had them within the previous year. You will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.

The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Elston Seal, M.D. (919) 966-6217. A licensed physician will be on call in the facility at all times. Other professional persons who work with them may assist or act for them.

In the event of physical injury directly resulting from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act or by the University of North Carolina at Chapel Hill. All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the researchers will assist me in obtaining appropriate medical treatment but the university of North Carolina at Chapel Hill does not provide financial assistance for medical or other costs. In the event that a physical injury is proximately caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 U.S.C. 2671-1680). You do not waive any liability rights for personal injury by signing this form.

This project has been approved by the Committee on the Protection of the Rights of Human Subjects at the University of North Carolina at Chapel Hill. If you believe that there is any infringement upon my rights, you may contact the chairman of the Committee, Ernest N. Kraybill, M.D., (919) 966-1344.

I have read the information provided above. I have had the opportunity to ask, and have had answered, all my questions about this research. I voluntarily agree to participate in this study. After it is signed I understand I will receive a copy of this consent form.

Signature of Research Subject

Date

Signature of Person Obtaining Consent

Date

UNC Hospitals
Chapel Hill, North Carolina

UNC-CH Study # 91-EPA-224

CONSENT FORM

APPROVED BY:

8-22-95 ENK-10

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D. (966-5049)
Coinvestigator: Shu-Chieh Hu, Ph.D. (966-6227)
Howard Kehrl, M.D. (966-6208)

You are asked to participate in a research study whose purpose is to investigate how much of inhaled particles deposit in the bronchial airways and how the lung deposition changes with the size of aerosol particles you are inhaling and the pattern of breathing. You will be one of approximately 150 subjects in this research study.

- A). Your participation in this study will require three visits on separate days and during the course of this study, the following will occur:
1. You will have a medical history, personality profile, physical examination, and a blood screening test administered to you prior to your selection as a subject.
 2. On your first visit to the laboratory, you will have a series of standard clinical tests to measure physiological functions of your lung after a brief training session (about one hour). If your lung function test results meet the criteria of this study, you will be asked to inhale test aerosols in a prescribed manner (about 6 hours).
 3. On your second visit, after lung function tests you will inhale, in a prescribed manner (same as the first visit), about two hundred breaths of test aerosols. The study will take about 6 hours.

4. On your third visit, you will inhale test aerosols in the same manner as the second visit. The study will take about 6 hours.

B). The following risks may be associated with this study:

1. Blood sampling (venipuncture) may cause some discomfort at the puncture site, but will not affect your health. The amount of blood withdrawn will approximately equal three tablespoons and should not adversely affect your health.

2. The inhalation of di-(2-ethylhexyl) sebacate (DEHS) oil may have a minimal risk to your health. The amount of DEHS oil that you will inhale on each test day is about 50 μ g that is about 1/20 of the amount that has been shown to have no toxicological effects in animals. If you are an asthmatic or a person with chronic bronchitis, the lung dose of inhaled aerosol may be substantially greater than the values given above depending on the severity of your abnormal lung conditions. The oil aerosol has been used for inhalation studies in both normals and persons with obstructive lung disease for a decade and no adverse health effects have been reported.

3. When you are required to have a bronchial challenge test, the inhalation of methacholine or histamine aerosols will cause a mild bronchial constriction. This may cause a feeling of "tightness" within your chest. This feeling should disappear in about 30 minutes. However, in any events that you feel uncomfortable and want to be treated, you will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. You may also feel a slight throat irritation which may make you cough. The irritation is transient and usually disappears in about 15 min. With histamine aerosols, you may notice flushing, rapid heart beat, lightheadedness (dizziness), or mild headache, all of which are transient.

4. Some risks are unforeseeable in participating in this study.

C). Exclusions and Termination:

1. If you are female, you will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If you are pregnant or have any reason to believe that you may be pregnant, you may not participate in the study.

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E) Benefits:

You will be paid \$10.00 per hour for your participation in this study. In addition, you will receive \$10.00 as a bonus for arriving promptly at the appointed time. You will also receive \$20.00 when you complete the initial screening and physical examination if you have not had them within the previous year. You will receive a check for the appropriate amount upon completion or termination (by either party) of the experiment.

The principal investigator responsible for the health and safety of the participation in this study is Chong S. Kim, Ph.D. (919) 966-5049. The physician responsible for the health and safety of the participants in this study is Elston Seal, M.D. (919) 966-6217. A licensed physician will be on call in the facility at all times. Other professional persons who work with them may assist or act for them.

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I have read the information provided above. I have had the opportunity to ask, and have had answered, all my questions about this research. I voluntarily agree to participate in this study. After it is signed I understand I will receive a copy of this consent form.

Signature of Research Subject

Date

Signature of Person Obtaining Consent

Date

UNC Hospitals
Chapel Hill, North Carolina

UNC-CH Study # 91-EPA-226

CONSENT FORM

APPROVED ON:

8-28-96 ENK-1c

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Determination of Deposition Dose of Inhaled Particles in Human Lung Airways

Principal Investigator: Chong S. Kim, Ph.D. (966-5049)
Coinvestigator: Shu-Chieh Hu, Ph.D. (966-6227)
Howard Kehrl, M.D. (966-6208)

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3. When you are required to have a bronchial challenge test, the inhalation of methacholine or histamine aerosols will cause a mild bronchial constriction. This may cause a feeling of "tightness" within your chest. This feeling should disappear in about 30 minutes. However, in any events that you feel uncomfortable and want to be treated, you will be given a bronchodilator drug (i.e., metaproterenol) that reverses the airway constriction quickly. You may also feel a slight throat irritation which may make you cough. The irritation is transient and usually disappears in about 15 min. With histamine aerosols, you may notice flushing, rapid heart beat, lightheadedness (dizziness), or mild headache, all of which are transient.

4. Some risks are unforeseeable in participating in this study.

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1. If you are female, you will be asked for a menstrual history and asked to provide a urine specimen for a pregnancy test. The results of this test will be held in strict confidentiality. If you are pregnant or have any reason to believe that you may be pregnant, you may not participate in the study.

2. Your participation is voluntary. You may refuse to participate, or discontinue your participation at any time without penalty, or losing benefits you would otherwise be entitled to.



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
The School of Medicine
(919) 966-1344

The University of North Carolina at Chapel Hill
CB# 7000, MacNider Building
Chapel Hill, N.C. 27599-7000

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
Carolina Campus,

FROM: John C. Herion, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: January 8, 1992

SUBJECT: AMENDMENT to: 91-EPA-226
Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This amendment has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects on January 8, 1992. The complete proposal, including the amendment, is due for re-review on October 25, 1992.

A brief description of this amendment is attached.

NOTE: If required by this amendment, a revised approved consent form is enclosed.

John C. Herion, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
The School of Medicine
(919) 966-1344

The University of North Carolina at Chapel Hill
CB# 7000, MacNider Building
Chapel Hill, N.C. 27599-7000

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS,

FROM: John C. Herion, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: February 5, 1992

SUBJECT: AMENDMENT to: 91-EPA-226
Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This amendment has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects on February 5, 1992. The complete proposal, including the amendment, is due for re-review on October 25, 1992.

A brief description of this amendment is attached.

NOTE: If required by this amendment, a revised approved consent form is enclosed.

A handwritten signature in cursive script, appearing to read "John C. Herion", written over a horizontal line.

John C. Herion, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
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Committee on the Protection
of the Rights of Human Subjects
The School of Medicine
(919) 966-1344

The University of North Carolina at Chapel Hill
CB# 7000, MacNider Building
Chapel Hill, N.C. 27599-7000

amendment

February 5, 1992

91-EPA-226 Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

To facilitate subject recruitment and laboratory scheduling, the protocol has been changed to require four three-hour sessions instead of two full-day sessions. This change does not affect the experimental procedures. The informed consent form has been appropriately modified. This is given expedited review.

A handwritten signature in cursive script, reading "John C. Herion", written over a horizontal line.

John C. Herion, M.D.
Chair of the Committee

JCH:bsb



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
(919) 966-1344
FAX (919) 966-7879

The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7000, 454 MacNider Building
Chapel Hill, NC 27599-7000

MEMORANDUM

TO: Chong S. Kim, Ph.D. *ENK*

FROM: Ernest N. Kraybill, M.D., Chair, Committee on the
Protection of the Rights of Human Subjects

DATE: September 2, 1993

SUBJECT: 91-EPA-226 Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

An approval letter for renewal of this study is enclosed. This includes approval of your request to repeat the histamine challenge in seven previously enrolled subjects. Subjects will be reminded of the risks associated with this procedure and will be paid \$10.00 per hour.



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
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(919) 966-1344
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The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7000, 454 MacNider Building
Chapel Hill, NC 27599-7000

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: November 15, 1993

SUBJECT: AMENDMENT to: 91-EPA-226
Determination of Deposition Dose of Inhaled Particles in Human
Lung Airways

This amendment has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects on November 12, 1993. The complete proposal, including the amendment, is due for re-review on September 2, 1994.

A brief description of this amendment is attached.

NOTE: If required by this amendment, a revised approved consent form is enclosed.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
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Committee on the Protection
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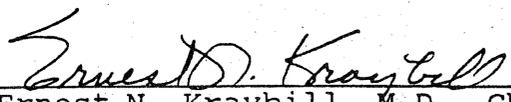
The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7000, 454 MacNider Building
Chapel Hill, NC 27599-7000

amendment

November 15, 1993

91-EPA-226 Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This amendment permits the substitution of chemical grade methacholine for the previously-used, FDA-approved Provocholine which is no longer available.


Ernest N. Kraybill, M.D., Chair
The Committee on the Protection
of the Rights of Human Subjects



THE UNIVERSITY OF NORTH CAROLINA
AT
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The School of Medicine
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Committee on the Protection
of the Rights of Human Subjects
(919) 966-1344
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TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: June 24, 1994

SUBJECT: AMENDMENT to: 91-EPA-226
Determination of Deposition Dose of Inhaled Particles in Human
Lung Airways

This amendment has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects on June 24, 1994. The complete proposal, including the amendment, is due for re-review on September 2, 1994.

A brief description of this amendment is attached.

NOTE: If required by this amendment, a revised approved consent form is enclosed.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
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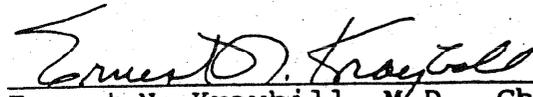
The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7000, 454 MacNider Building
Chapel Hill, NC 27599-7000

amendment

June 24, 1994

91-EPA-226 Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This amendment provides for the addition of dead space volume measurement by nitrogen washout method in 14 subjects, deletes the bronchial challenge, and adds continued aerosol inhalation for one minute after the bolus aerosol inhalation. The informed consent form has been appropriately revised. Risk is not altered. This is given expedited review.


Ernest N. Kraybill, M.D., Chair
The Committee on the Protection
of the Rights of Human Subjects

A deposit 12/15/95



THE UNIVERSITY OF NORTH CAROLINA
AT
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The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7000, 454 MacNider Building
Chapel Hill, NC 27599-7000

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: February 2 1995

SUBJECT: AMENDMENT to: 91-EPA-226
Determination of Deposition Dose of Inhaled Particles in Human Lung
Airways

This amendment has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects on February 2 1995. The complete proposal, including the amendment, is due for re-review on August 30 1995.

A brief description of this amendment is attached.

NOTE: If required by this amendment, a revised approved consent form is enclosed.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
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The School of Medicine
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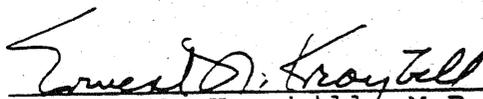
amendment

February 2, 1995

91-EPA-226

Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This amendment seeks to include patients with diagnoses of asthma, COPD, and heavy smoker subjects (20/group) and additional older normal subjects (20). The tests to be done are the same as those previously done in young normals and should pose little risk. This is given expedited review.


Ernest N. Kraybill, M.D., Chair
The Committee on the Protection
of the Rights of Human Subjects

Also reviewed by Robert A Mueller, M.D., Ph.D.



THE UNIVERSITY OF NORTH CAROLINA
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The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: August 22 1995

SUBJECT: AMENDMENT to: 91-EPA-226
Determination of Deposition Dose of Inhaled Particles in Human Lung
Airways

This amendment has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects on August 22 1995. The complete proposal, including the amendment, is due for re-review on August 8 1996.

A brief description of this amendment is attached.

NOTE: If required by this amendment, a revised approved consent form is enclosed.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

Committee on the Protection
of the Rights of Human Subjects
(919) 966-1344
FAX (919) 966-7879

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: May 15 1996

SUBJECT: AMENDMENT to: 91-EPA-226
Determination of Deposition Dose of Inhaled Particles in Human Lung
Airways

This amendment has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects on May 15 1996. The complete proposal, including the amendment, is due for re-review on August 8 1996.

A brief description of this amendment is attached.

NOTE: If required by this amendment, a revised approved consent form is enclosed.

Ernest N. Kraybill, M.D.
Chairman of the Committee



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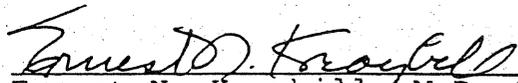
The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

amendment

May 15, 1996

91-EPA-226 Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This amendment will (1) add 20 young normal subjects (age <40 years) for a submicron particle study, (2) lower the FEV1/FVC ratio from 0.75 to 0.70 for normal subjects and (3) add 20 healthy older subjects having a slight lung function decrement - FEV1/FVC ratio between 0.60 and 0.70. The risk is no more than minimal. This is approved by expedited review.


Ernest N. Kraybill, M.D., Chair
The Committee on the Protection
of the Rights of Human Subjects



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Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: February 18 1998

SUBJECT: AMENDMENT to: 91-EPA-226
Determination of Deposition Dose of Inhaled Particles in Human Lungs

This amendment has been reviewed and approved by the Committee on the Protection of the Rights of Human Subjects on February 18 1998. The complete proposal, including the amendment, is due for re-review on August 14 1998.

A brief description of this amendment is attached.

NOTE: If required by this amendment, a revised approved consent form is enclosed.

A handwritten signature in cursive script that reads "Ernest N. Kraybill".

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
(919) 966-1344
FAX (919) 966-7879

The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

amendment

February 18, 1998

91-EPA-226

Determination of Deposition Dose of Inhaled Particles in Human
Lungs

This amendment adds three co-investigators, excludes subjects with cardiac or kidney disease or diabetes requiring insulin, reduces study procedures so that time requirement is reduced, makes other minor changes and clarifications, and provides a \$20 bonus for completion of the study. Risk is not increased. This is approved by expedited review.

A handwritten signature in cursive script, reading "Ernest N. Kraybill", written over a horizontal line.

Ernest N. Kraybill, M.D., Chair
The Committee on the Protection of the Rights
of Human Subjects



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

The School of Medicine
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CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

Committee on the Protection
of the Rights of Human Subjects
(919) 966-1344 FAX (919) 966-7879
www.med.unc.edu/irb/

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: The Committee on the Protection of the Rights
of Human Subjects

DATE: June 27 2000

SUBJECT: Research Application Review

STUDY: IRB# 91-EPA-226 Title: Determination of Deposition Dose of Inhaled
Particles in Human Lungs

This research proposal has been considered by the Committee and
has been approved until June 27 2001.

- (1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01.
- (3) Re-review of this proposal is necessary before:
 - (a) making any significant alterations or additions to the proposal, except when necessary to eliminate apparent immediate hazards to the subject, or
 - (b) continuing beyond the approval date.
- (4) It is required that all signed consent forms be retained on file.
- (5) Approved consent form(s) enclosed.

West N. Kraybill, M.D./Stephen A. Bernard, M.D.
Chairmen of the Committees



THE UNIVERSITY OF NORTH CAROLINA
AT
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The School of Medicine
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renewal

June 27, 2000

91-EPA-226

Determination of Deposition Dose of Inhaled
Particles in Human Lungs

This renewal, reviewed and approved by the Full Committee, includes an amendment making changes in payment to subjects, removes a co-investigator, increases the study population, and adds a substudy. The consent form is revised appropriately.

Ernest N. Kraybill, M.D./Stephen A. Bernard, M.D.
Chairmen of the Committees



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
The School of Medicine
(919) 966-1344

The University of North Carolina at Chapel Hill
CB# 7000, MacNider Building
Chapel Hill, N.C. 27599-7000

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
Carolina Campus,

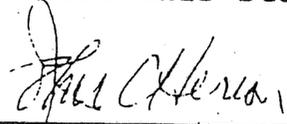
FROM: John C. Herion, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: October 25, 1991

SUBJECT: Research Application Review
Number: 91-EPA-226
Title: Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This research proposal has been considered by the Committee and it has been approved until October 25, 1992.

- NOTE:
- (1) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. Assurance Number: M-1390; IRB Number: 01NR.
 - (2) Re-review of this proposal is necessary if:
 - (a) Any significant alterations or additions to the proposal are to be made
 - (b) You wish to continue beyond the above date
 - (3) It is required that all signed consent forms be retained on file.
 - (4) A copy of the approved consent form is enclosed. This is the only consent form approved for this study.



John C. Herion, M.D.
Chairman of the Committee

Enclosure (e)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 18 1991

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Protection of Human Subjects

FROM: Ken Sexton, Sc.D.
Director
Office of Health Research (RD-683)

TO: Timothy R. Gerrity, Acting Chief
Clinical Research Branch
Human Studies Division
Health Effects Research Laboratory/RTP

I have reviewed the proposal and am satisfied that it complies with EPA Order 1000.17, Policy and Procedures for Protection of Human Subjects in Biomedical and Behavioral Research.

Item: "Determination of Deposition Dose of Inhaled Particles in Human Lung Airways" by Dr. Chong Kim



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
The School of Medicine
(919) 966-1344

The University of North Carolina at Chapel Hill
CB# 7000, MacNider Building
Chapel Hill, N.C. 27599-7000

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: September 3, 1992

SUBJECT: Research Application Review

Number: 91-EPA-226

Title: Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This research proposal has been considered by the Committee and
it has been approved until September 3, 1993.

- NOTE:
- (1) Review Type: Full Committee
 - (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01NR.
 - (3) Re-review of this proposal is necessary if:
 - (a) Any significant alterations or additions to the proposal are to be made
 - (b) You wish to continue beyond the above date
 - (4) It is required that all signed consent forms be retained on file.
 - (5) A copy of the approved consent form is enclosed. This is the only consent form approved for this study.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
(919) 966-1344
FAX (919) 966-7879

The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7000, 454 MacNider Building
Chapel Hill, NC 27599-7000

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: September 2, 1993

SUBJECT: Research Application Review

Number: 91-EPA-226

Title: Determination of Deposition Dose of Inhaled Particles in Human
Lung Airways

This research proposal has been considered by the Committee and
it has been approved until September 2, 1994.

- (1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01NR.
- (3) Re-review of this proposal is necessary if:
 - (a) any significant alterations or additions to the proposal are to be made, and/or
 - (b) you wish to continue beyond the approval date.
- (4) It is required that all signed consent forms be retained on file.
- (5) A copy of the approved consent form is enclosed. This is the only consent form approved for this study.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Deposit

Committee on the Protection
of the Rights of Human Subjects
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The University of North Carolina at Chapel Hill
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Chapel Hill, NC 27599-7000

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: August 30, 1994

SUBJECT: Research Application Review

Number: 91-EPA-226

Title: Determination of Deposition Dose of Inhaled Particles in Human
Lung Airways

This research proposal has been considered by the Committee and
it has been approved until August 30, 1995.

- (1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01NR.
- (3) Re-review of this proposal is necessary if:
 - (a) any significant alterations or additions to the proposal are to be made, and/or
 - (b) you wish to continue beyond the approval date.
- (4) It is required that all signed consent forms be retained on file.
- (5) Approved consent form(s) enclosed.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
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The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: August 8 1995

SUBJECT: Research Application Review

STUDY: IRB# 91-EPA-226 Title: Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This research proposal has been considered by the Committee and
it has been approved until August 8 1996.

- (1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01NF.
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 - (a) any significant alterations or additions to the proposal are to be made, and or
 - (b) you wish to continue beyond the approval date.
- (4) It is required that all signed consent forms be retained on file.
- (5) Approved consent forms enclosed.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
of the Rights of Human Subjects
(919) 966-1344
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The University of North Carolina at Chapel Hill
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Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: August 28 1996

SUBJECT: Research Application Review

STUDY: IRB# 91-EPA-226 Title: Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This research proposal has been considered by the Committee and
it has been approved until August 28 1997.

- 1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01NR.
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- (5) Approved consent form(s) enclosed.

Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
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Committee on the Protection
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Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: August 14 1997

SUBJECT: Research Application Review

STUDY: IRB# 91-EPA-226 Title: Determination of Deposition Dose of Inhaled
Particles in Human Lung Airways

This research proposal has been considered by the Committee and
it has been approved until August 14 1998.

- (1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01NF.
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Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
AT
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~~A-DEPOSIT~~
~~S-DEPOSIT~~

Committee on the Protection
of the Rights of Human Subjects
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The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: July 28 1998

SUBJECT: Research Application Review

STUDY: IRB# 91-EPA-226 Title: Determination of Deposition Dose of Inhaled
Particles in Human Lungs

This research proposal has been considered by the Committee and
it has been approved until July 28 1999.

- 1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01.
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Ernest N. Kraybill, M.D.
Chairman of the Committee



THE UNIVERSITY OF NORTH CAROLINA
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S-DEPOSIT

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FAX (919) 966-7879

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CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: Ernest N. Kraybill, M.D., Chairman of the Committee
on the Protection of the Rights of Human Subjects

DATE: July 13 1999

SUBJECT: Research Application Review

STUDY: IRB# 91-EPA-226 Title: Determination of Deposition Dose of Inhaled
Particles in Human Lungs

This research proposal has been considered by the Committee and
it has been approved until July 13 2000.

- (1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01.
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Ernest N. Kraybill, M.D.
Chairman of the Committee



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The School of Medicine
The University of North Carolina at Chapel Hill
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Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: The Committee on the Protection of the Rights
of Human Subjects

DATE: June 27 2000

SUBJECT: Research Application Review

STUDY: IRB# 91-EPA-226 Title: Determination of Deposition Dose of Inhaled
Particles in Human Lungs

This research proposal has been considered by the Committee and
has been approved until June 27 2001.

- (1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number: M-1390; IRB Number: 01.
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- (4) It is required that all signed consent forms be retained on file.
- (5) Approved consent forms enclosed.

est N. Kraybill, M.D. Stephen A. Bernard, M.D.
irmen of the Committees



THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Committee on the Protection
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The School of Medicine
The University of North Carolina at Chapel Hill
CB# 7097, Medical School Building 52
Chapel Hill, NC 27599-7097

TO: Chong S. Kim, Ph.D.
EPA Health Effects Res. Lab.
CB# 7310 Med. Res. Bldg. C
CAROLINA CAMPUS

FROM: The Committee on the Protection of the Rights
of Human Subjects

DATE: June 26 2001

SUBJECT: Research Application Review

STUDY: IRB# 91-EPA-226 Title: Determination of Deposition Dose of Inhaled
Particles in Human Lungs

This research proposal has been considered by the Committee and
it has been approved until June 26 2002.

- (1) Review Type: Full Committee
- (2) This Committee complies with the requirements found in Part 56 of the 21 Code of Federal Regulations and Part 46 of the 45 Code of Federal Regulations. The assurance of compliance with DHHS regulations is on file in the Committee office for your perusal. Assurance Number:M-1390; IRB Number: 01.
- (3) Re-review of this proposal is necessary before:
 - (a) making any significant alterations or additions to the proposal, except when necessary to eliminate apparent immediate hazards to the subject, or
 - (b) continuing beyond the approval date.
- (4) It is required that all signed consent forms be retained on file.
- (5) Approved consent form(s) enclosed.

Stephen A. Bernard, M.D.
Chairman of the Committees

III. Required education in Human Subject Protection

The following individuals have completed educational experiences on the protection of human subjects in research that meet the requirements of the National Institutes of Health and the University of North Carolina at Chapel Hill:

Kim, Chong
Kehrl, Howard

All the above individuals are listed in a training database maintained by the Office of Research Services. The database contains information about the specific educational experiences completed, and the office also maintains written documentation of those experiences.

These names can be verified on the World Wide Web at <http://zeppo.admin.unc.edu/isapi/certweb.dll>

IV. Potential Conflict of Interest

Not applicable.

September 6, 2001

Stephen A. Bernard, M.D., Chair
Committee on the Protection
of the Rights of Human Subjects
The School of Medicine
The University of North Carolina at Chapel Hill
CB #7097, Medical Building 52
CAROLINA CAMPUS

Dear Dr. Bernard:

On August 16, 2001, the EPA Human Studies Division management was informed that some subjects enrolled in Dr. Kim's study 91-EPA-226, entitled: "Determination of Deposition Dose of Inhaled Particles in Human Lungs" had been inadvertently exposed to a greater particle mass than had been stated in the calculation of dose in the approved research protocol and specified in the consent form.

As soon as this discovery was made, I contacted Dan Nelson to inform him that we had discovered this violation, that we were shutting down the study, that no one we were aware of had been injured, and that we would follow the verbal notification with a detailed report of the incident and our investigation. This is that report. On August 26, I also sent notification in writing of the shut down of the study to you. In addition, EPA management in the Human Studies Division notified EPA management at the first level above our Division (Associate Director for Health, National Health and Environmental Effects Research Laboratory), and at the second level above (Laboratory Director, National Health and Environmental Effects Research Laboratory).

Investigation reveals that up to 50, but probably fewer, subjects may have been exposed to a greater dose of the test material (di-2-ethylhexyl sebacate, an inert product used extensively over the past 20 years in many laboratories) than permitted in the protocol or than the subjects agreed to. The maximum dose any subject may have been exposed to is approximately 1.5 milligrams.

The study examines deposition fraction of particles in the lungs as a percentage of inhaled dose, not as a quantified dose. The study began in 1992 with small particles and simple breathing patterns, but through a series of amendments over the years, progressed to larger particles and

Enclosure (g)

more complex breathing patterns which caused more material to be inhaled and therefore deposited without determining exactly the quantity of material that would be deposited in the subjects' lungs.

This is the second instance of a human research protocol violation in the past four years by the principal investigator, Dr. Kim. On December 15, 1997, I informed Dr. Ernest Kraybill and the Committee of a previous infraction for which Dr. Kim received a written warning by his supervisor. Dr. Kim assured Human Studies Division management that he would not again violate the terms of a human research protocol.

We also took this opportunity to review Dr. Kim's study as well as all clinical studies on-going in the Division, and were very disturbed by other findings in the review of Dr. Kim's study. He has appropriately signed consent forms for only 100 of the 118 studies. In 17 of 18 cases of unsigned consent forms, only the subject's signature appears on the consent form; in the remaining case neither the subject's signature nor the signature of the person obtaining consent appears on the form. We find the lack of documentation of signed informed consent to be very concerning. We have now taken steps to periodically audit the consent forms of all human research to be certain that the forms are signed appropriately.

A review of all other studies on-going in the Human Studies Division, reveals that this problem is unique to Dr. Kim's protocol and is not a problem systemic to our research program.

In at least one case, we have noted that an individual associated with Dr. Kim's study has not been updated on the protocol or consent form. However, this individual does have IRB approval as a co-investigator on several approved UNC studies. We have taken steps to be sure that all individuals associated with a protocol throughout the life of the study will be reported to the Committee. This measure is taken, in part, to assure the Committee that investigators involved in studies provide evidence that they have received the required training in human research.

At the Division level, a number of changes are underway to assure the protection of the human research subjects who participate in our studies, including additional review of protocols and consent forms, round table critiques of protocols under development, and a greater willingness of management to be involved in human research issues. I also believe that repeated amendments which change the fundamental nature of a study cannot be allowed and have taken steps at the Division level to assure that changes of a fundamental nature will require the submission of a new protocol.

As for the individual who unintentionally but negligently disregarded the requirements of ethical human research, Human Studies Division management has made the decision to ban Dr. Kim indefinitely from the conduct of human research. We are working with our Personnel Department on formal disciplinary action.

We would appreciate the input of the Committee on whether to notify the subjects involved in the inadvertent over exposure. We are convinced, following an external estimate of the risk associated with the highest dose, that no subject was harmed. [Fred Miller has promised a verbal

report by tomorrow (9-7-01) and a written report by Monday (9-10-01)] We believe that full disclosure is very important. Nevertheless, we don't want to unnecessarily alarm subjects either. We are prepared to do whatever the Committee's recommends.

We regret that these protocol violations have occurred, but have seen this as an opportunity to strengthen our protections for human research subjects by instituting a series of new policies and procedures in the Human Studies Division.

Sincerely,

Elston Seal, Jr., M.D.
Human Subjects Research Review Official,
National Health and Environmental Effects Research Laboratory

cc

James Samet
Linda Birnbaum
Harold Zenick
Lawrence Reiter

March 27, 2002

Committee on the Protection
of the Rights of Human Subjects
The School of Medicine
The University of North Carolina
CB# 7097, Medical School Building 52
Carolina Campus

Dear Members of the Committee:

On several previous occasions I have contacted you both in writing and orally to inform you of a violation of an approved human research protocol by one of the investigators in the EPA Human Studies Division, Dr. Chong Kim.

After an exhaustive analysis of the dose of di-2-ethylhexyl sebacate ("sebacate oil") that each subject received, we believe that subjects were indeed exposed to more than the amount stated in the protocol and informed consent form. However, the amount they were exposed to is not higher than the concentration used in some other human studies (for further information, please see the reference attached), and this amount has not caused untoward effects humans.

We are now preparing to contact the subjects who received sebacate oil in a dose that was greater than the amount specified in their informed consent form. A draft of a proposed letter is attached. We would greatly value your constructive criticism of this letter, if possible, by April 5, 2002.

After we have contacted the research subjects by letter, I will again write to you to bring the members of your Committee up to date on our continued handling of this incident.

Very truly yours,

Elston Seal, Jr., M.D.
Human Subjects Research Review Official,
National Health and Environmental Effects Research Laboratory

attachment

Reference: P. Brand, I. Frimmel, T. Meyer, H. Schultz, J. Heyder, K. Haubinger. Total deposition of therapeutic particles during spontaneous and controlled inhalations. J. Pharmaceutical Sciences 89: 724-731, 2000.



June 4, 2002

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

OFFICE OF
RESEARCH AND DEVELOPMENT

In August 1998, you participated in a study ("Adeposit/Sdeposit") at the U.S. Environmental Protection Agency's Human Research Facility in Chapel Hill, NC. As part of the study, you may recall that you were asked by the person in charge of the study to inhale very fine particles. The type of particle you inhaled was a material called di-2-ethylhexyl sebacate ("sebacate oil"), which is a nontoxic material that has been used for more than twenty years in laboratories around the world in similar breathing studies with both humans and animals.

We have recently discovered that the amount of material you breathed, while entirely within safe limits, inadvertently exceeded by 30 to 50 times the amount that was described in the consent form which you signed before participating in the study. Because the dose exceeded the amount specified in the consent form, we wanted to inform you of this difference.

The material is safe for human consumption, even at the elevated doses you received, based on many studies conducted both in this and other laboratories. In other studies, humans have been exposed to similar concentrations of sebacate oil particles as you received with no reported ill effects. In addition, animals have been exposed to concentrations of sebacate oil in amounts much higher than you received with no ill effects. This is a primary reason that this material has been used so widely for this type of research. Since the study ended, no study participant has reported any symptoms to us related to exposure to di-2-ethylhexyl sebacate. We feel, however, that you should know about the difference in dose from the amount described in the consent form and the actual dose you received.

We sincerely regret that this error occurred and have implemented changes to be certain that it does not happen again. If you would like additional information or would like to discuss this event with a physician, please call Dr. Elston Seal at (877) 854-8864. He will be glad to discuss any questions you might have.

Very truly yours,

Harold Zenick, Ph.D.
Associate Director for Health

STANDARD/RECOMMENDED OPERATING PROCEDURE FOR
Generation of Monodisperse Aerosols
SOP No. NHEERL-H-HSD-CRB-CSK/95-601-000

This Standard Operating Procedure has been prepared for the sole use of the National Health & Environmental Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, and may not be specifically applicable to the activities of other organizations.

Author: Chong E. Lee (signature/position) Date 7/3/95

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^c Signature documents the review if no revisions are required.

GENERATION OF MONODISPERSE TEST AEROSOLS WITH VIBRATING ORIFICE AEROSOL GENERATOR

Chong Kim, July 3, 1995

1. SCOPE OF APPLICATION

This protocol is a condensed version of the manufacturer's operating manual and will provide a quick guidance of generating monodisperse test aerosols with a vibrating orifice aerosol generator. Detailed procedures must be found in the manufacturer's operating manual.

2. PREREQUISITES

2.1 Equipment

Vibrating orifice aerosol generator (Model 3050, TSI Inc. St. Paul, MN) which consists of
Vibrating crystal assembly
Signal generator (model E310-B, Dynascan Corp.)
Liquid feed pump (model 975, Harvard Apparatus)
Kr-85 aerosol neutralizer (model 3054, TSI, Inc.)
Rotameters (Dwyer Instruments)
Filter holder for cartridge HEPA filter
Air pressure regulator (0-100 psi range)

2.2 Supplies

HEPA filter
Compressed air supply (at least 100 liters/min flow at 50 psi)
Syringes (20 and 50 ml)
Filter holder (10 mm diameter) connectable to the syringe tip
0.5 μ m pore liquid filter (Fluoropore 10 mm diameter)

2.3 Training

In-house training by a supervisor is needed.

3. CAUTIONARY NOTES OR SPECIAL CONSIDERATION

The vibrating orifice aerosol generator is the "primary" aerosol generator which produces the standard particles to be used for instrument calibrations. Every generator setting and aerosol solution must be exact. The liquid orifice must be kept from plugging. It is not tolerable even a minute leakage of solution from the feeding system. Avoid an excessive pressure buildup in the syringe pump by replacing the liquid filter frequently.

To avoid fire hazard when a combustible volatile solvent is used, the dilution air flow should always be sufficient to keep the combustible vapor below the explosion limit and the generator should be used in a well-ventilated space.

4. PROCEDURE

4.1 System Checkup

1. Check the coaxial cable with BNC connectors between the signal generator and main body of the aerosol generator.
2. Check the signal cable and the dispersion air tube inside the aluminum support column.

3. Check the connection of liquid feed tube to the base of the orifice.
4. Check if the rubber stopper around the Teflon liquid feed tube and drain tube is plugged firmly into the hole on the side of the aluminum support column.
5. Check the compressed air supply line.

4.2 Generator Settings

1. In the signal generator:
Function: sine wave
Output level: Middle
Attenuators: off
Frequency: 30-110 kHz for 20 μ m diameter orifice. Set the frequency determined by theoretical calculation (see 4.6 calculation).
2. Set the gear position at #16 in the liquid feed pump.
3. In the main body of the generator:
Air pressure: 20-30 psi
Dispersion air flow rate: 1.5 lpm
Dilution air flow rate: 100 lpm (or 6 m³/h)

4.3 Running Steps

1. Turn off the signal generator and compressed air supply
2. Flush the liquid feed system with reagent grade isopropyl alcohol. Place a 20 ml syringe filled with alcohol in the liquid feed pump and run the pump at a gear position #3 or #4.
3. Repeat step 1 but stop feeding alcohol at a half way through and plug up the drain tube.
4. Remove the dispersion air cap to expose the piezoelectric ceramic and the orifice assembly.
5. Start the syringe pump and momentarily place the pump in gear position #1 (for one or two seconds only). When the liquid begins to squirt through the orifice, switch the gear to position #16. **It will take about 3 minutes for the liquid flow rate through the orifice to become steady after shifting the pump gear.**
6. Turn on the signal generator and compressed air supply. Close off the dilution air.
7. Check the uniformity of alcohol droplets by attaching a small stainless steel elbow to the dispersion air outlet. While observing the deflection pattern of the droplet stream, adjust the frequency to obtain a single monodisperse stream.
8. Stop the liquid pump and remove the alcohol syringe.
9. Flush the liquid feed system with aerosol solution in the same way as the initial flushing with alcohol (step 2).
10. Refill the syringe with an aerosol solution (Appendix A) and feed the solution through the orifice in the same way as step 5.
11. Check the uniformity of droplets by observing the jet deflection (same as step 7).
12. Place the dispersion cap over the piezoelectric crystal assembly.
13. Place the dilution air column.

4.4 Quality Control and Evaluation Criteria

Output aerosols are monitored with an optical particle counter linked to a multichannel analyzer in which the size distribution of aerosols is displayed graphically on the monitor screen. Monodispersity of the aerosol is judged by a narrow single peak and particle diameter is determined by the channel number of the peak. As an alternative method,

aerosols are sampled into the aerodynamic particle sizer and the complete size distributions are obtained.

Presence of more than a single peak indicates the aerosol contains particles with different sizes. If multiple peaks are observed, the dispersion test of the jet stream must be repeated and corrective actions (see section 4.5) must be taken to obtain a single peak distribution. The channel number of the peak should not shift more than $\pm 5\%$ during operation.

4.5 Corrective Actions

If multiple peaks are observed in the multichannel analyzer, repeat the dispersion test of jet stream. Adjust the frequency until a single jet stream is obtained and satellites are disappeared. If the jet stream is single and narrow in width, but satellites are persistent, increase the signal amplitude gradually until satellites are disappeared.

4.6 Calculation

The diameter of solution droplets ejected from the orifice is determined by the following theoretical equation:

$$D_d = (6Q/\pi f)^{1/3}$$

Where Q is the liquid feed rate (ml/s) and f is the vibrating frequency (Hz). If a solution containing a non-volatile solute in a volatile solvent is sprayed through the orifice and the solvent is allowed to evaporate from the droplets, non-volatile particles of the solute are obtained. The particle diameter is determined by

$$D_p = C^{1/3} D_d$$

Where C is the volumetric concentration of the solute in the solution and D_d is the droplet diameter calculated by the above equation.

4.7 Record Keeping

All the raw data including generator settings, peak channel number, and solution concentration are recorded in the laboratory notebook. The data are also inputted into the computer worksheet to calculate the D_d and D_p . Particle size distribution results obtained with APS are recorded in the laboratory notebook and computer printouts are kept in a separate file.

5. PERTINENT REFERENCES

Manufacturer's operating manual must be used for further details.

6. APPENDICES

Appendix A: Preparation of aerosol solutions

APPENDIX A

PREPARATION OF AEROSOL SOLUTIONS

1. SCOPE OF APPLICATION

This procedure is intended to provide a general guideline for preparing solutions of non-critical materials.

2. PREREQUISITES

2.1 Equipment and Supplies

Microbalance (1 mg reading accuracy, model R200D, Sartorius Corp.)

Volumetric flask (100, 250 and 500 ml)

Parafilm

Weighing dish

Spatula

Funnel (polyethylene or borosilicate glass)

Oleic acid (other aerosol materials)

Sodium fluorescein (or uranine)

Isopropyl alcohol

Distilled and deionized water

Disposable pipettes (1-20 ml TD range)

Pipette pump

2.2 Training

Basic chemistry laboratory training is required.

3. PROCEDURE

3.1 Untagged Solutions

1. Transfer approximately 300 ml of reagent isopropyl alcohol into a 500 ml volumetric flask using a funnel.

NOTE: When a smaller size flask is used, see Step 6

2. Transfer a predetermined amount of oleic acid (or other liquid aerosol materials) into the flask using a rubber pipette pump (for example, 5 ml of oleic acid for 1% solution, see section 3.3 Calculation below).
3. Shake the mixture and add alcohol gradually to the 500 ml fill line.
4. Seal the flask with parafilm and rotate the flask a half way up and down a few times to enhance mixing.
5. Place a label on the flask.
6. In order to prepare solutions less than 500 ml use a smaller volume flask (100 or 250 ml) and repeat above steps with each quantity proportionally reduced.

NOTE: The label must include the amount and names of solute and solvent, date of preparation, and initials of preparer.

3.2 Uranine Tagged Solutions

NOTE: To prepare a mixed solution of oleic acid and uranine maintain the ratio of oleic acid to uranine in the solution to be approximately 9 to 1. For example, add 0.9 ml of oleic acid and 0.1 gram of uranine to prepare 100 ml of 1% mixed solution.

1. Prepare 1% uranine stock solution in distilled and deionized water following the steps described in section 3.1. Here, instead of 5 ml of oleic acid shown in the step 2 above, add 5 grams of uranine weighed with a Sartorius balance.
2. To prepare 500 ml of 1% mixed solution, follow the steps described for untagged solution in section 3.1, but add 4.5 ml of oleic acid and 50 ml of 1% uranine stock solution prepared above instead of 5 ml of oleic acid.

NOTE: In preparing for a mixed solution, using a uranine stock solution will avoid a laborious weighing procedures for uranine powder.

3.3 Calculation

The following is the basic equation to determine concentrations of common solutions:

$$\% \text{ concentration} = 100 \times \frac{V_{\text{solute}}}{(V_{\text{solute}} + V_{\text{solvent}})}$$

where V is the volume (ml). Therefore, to prepare a 1% oleic acid solution in isopropyl alcohol, add 1 ml of oleic acid in 99 ml of isopropyl alcohol as

$$1\% = 100 \times (1 \text{ ml oleic acid}) / (1 \text{ ml oleic acid} + 99 \text{ ml isopropyl alcohol})$$

In order to prepare solutions with solid materials, use mass (in grams) of solute, instead of volume, in the above equation.

3.4 Record Keeping

All of the raw data including the volume or mass of solutes and solvents are recorded in the laboratory notebook. Steps of calculations to determine the amounts of ingredients are also recorded.

STANDARD/RECOMMENDED OPERATING PROCEDURE FOR
Operation of CI-7700 optical Particle Counter
SOP No. NHEERL-H-HSD-GRB-CSK/95-000
 602

This Standard Operating Procedure has been prepared for the sole use of the National Health & Environmental Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, and may not be specifically applicable to the activities of other organizations.

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OPERATION OF CI-7300 CLIMET OPTICAL PARTICLE COUNTER AND MULTICHANNEL ANALYZER

Chong Kim, June 28, 1995

1. SCOPE OF APPLICATION

This procedure is intended to be a quick guide for operating a CI-7300 Optical Particle Counter. Detailed procedures must be found in the manufacturer's operating manual.

2. PREREQUISITES

2.1 Equipment and Supplies

Climet optical particle counter (model CI-7300, Climet Instruments, Co.)
Aerosol diluter
Absolute cartridge filter
Multichannel analyzer (model 3502, Canberra Industries, Inc.)
Coaxial cables with BNC connectors
Personal computer
Printer

2.2 Training

In-house training by a supervisor is necessary.

3. CAUTIONARY NOTES OR SPECIAL CONSIDERATIONS

Because the optical particle counter (OPC) detects particles one by one, aerosol concentration must not exceed about 200 particles/cc. If concentrations are too high, multiple particles are counted as a single large particle.

WARNING: The lower detection limit of the OPC is 0.3 micron diameter. Attempting to measure particles in the size range near the detection limit will result in unreliable outcome.

4. PROCEDURE

4.1 System Checkup

1. Check the connection of a coaxial signal cable between the "analog output" port on the back panel of OPC and "ADC IN" of multichannel analyzer (MCA).
2. Set "ADC IN" switch to "EXT" position on the back panel of the MCA

4.2 Start Up of OPC

1. Turn on power switch on the back panel.
2. Turn on pump by pressing FCTN and PUMP POWER keys in sequence on the keypad.

NOTE: After pressing the FCTN key, three seconds are given to press the second key. If the key is not pressed within three seconds, OPC will not recognize the second key. The beeper will sound to indicate time-out. If time-out occurs, press FCTN again and then the second key.

3. Select Display by pressing the FCTN and Display 1, 2, or 3 keys.
Select Display 1 or 2 for particle counting
Select Display 3 to see time and date, flow indication, time delay, and statistics
4. Press FCTN and TOTAL/DIFF keys and set the counting mode for total or differential counting.
5. Press FCTN and SAMPLE TIME keys and set the sampling time for 1 minute.

NOTE: The sample time can be adjusted depending on aerosol concentration, longer for low concentration aerosols and shorter for high concentration aerosols.

6. Press START key to start sampling. A red indicator light is on during active sampling.
7. Observe the number of particles counted on DISPLAY screen.
8. Press STOP key to terminate the sampling process.

NOTE: STOP does not reset the counters or clear the displayed counts.

9. Press RESET key to start a new sample process, if one is not in progress or to terminate a sample process and begin a new one.

NOTE: RESET clears the counts shown on the display and resets all preset parameters.

4.3 Start Up of MCA

1. Turn on power switch located on the rear panel.
2. A few seconds after power on, the display screen will appear.
3. Type in correct time and date using the numeric key pad. Press CLR to erase the entered value and STORE to register the value.
Time format: Hours.Minutes (24 hour basis)
Date format: DD.MM.YY
4. Press YES to have new values accepted. The system's normal display will appear.
5. Check the MCA settings
PHA: positive input
MCSR: off
M/R: off
Vertical Range: 1K (if necessary, adjust to higher values up to 1048K)
Memory: 1/4 or 1/2
ADC Gain: 4096
ADC Offset: None
Amplifier Gain: Fine 0.3, Coarse 900
6. Press COLLECT to start sampling.

NOTE: In order for MCA to collect samples, OPC must be in the active sampling mode.

7. Observe frequency spectrum on the monitor screen.
8. If spectrum rises too fast, increase the vertical gain.
9. Press COLLECT key to terminate sampling.

NOTE: For PHA operations, the voltage range to be analyzed is 0-10 volt. Therefore, input signals greater than 10 volts cannot be analyzed. Resolution of the analysis is determined by a selection of ADC gain. The maximum resolution can be obtained by selecting ADC gain equal to the memory size. For a 4K memory, this corresponds to an ADC gain of 4096.

5. PERTINENT REFERENCE

Manufacturer's manuals must be used for further details of operation.

STANDARD/RECOMMENDED OPERATING PROCEDURE FOR
Sampling & Analysis of Aerosols for Model Studies
SOP No. NHEERL-H-HSD-CRB-CSK/95/03000

This Standard Operating Procedure has been prepared for the sole use of the National Health & Environmental Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, and may not be specifically applicable to the activities of other organizations.

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^c Signature documents the review if no revisions are required.

SAMPLING AND ANALYSIS OF AEROSOL PARTICLES FOR AIRWAY MODEL DEPOSITION STUDIES

Chong Kim, July 3, 1995

1. SCOPE OF APPLICATION

This operating procedure is to be followed unless specific deviations are detailed in the protocol for an individual experiment.

2. PREREQUISITES

2.1 Equipment

Bifurcating airway models (single and double bifurcation models)

Open face filter holders (47 mm diameter)

Rotameters (0-1, 0-5, 0-10 lpm ranges, Dwyer Instruments, Michigan City, IN)

Fluorometer (model 112, Sequoia-Turner Corp.)

Cuvettes and cuvette holder

Beakers (50, 100, and 400 ml capacity)

Funnels and funnel holders

Laboratory stand

Three-prong clamps and clamp holders

Vacuum pump

Tygon tubing (1/4" ID)

Ultrasonic cleaner

Precision liquid dispenser (0-10 ml capacity with 0.1 ml accuracy)

Timer (0-60 min with 1 sec. accuracy)

2.2 Supplies

Fluoropore filter (0.5 μm pore, 47 mm diameter, Millipore Corp.)

Durapore filter (0.45 μm pore, 47 mm diameter, Millipore Corp.)

Compressed air

Purified deionizer water

2.3 Training

Basic laboratory training is required by a supervisor.

3. CAUTIONARY NOTES OR SPECIAL CONSIDERATION

Because very low concentrations of a fluorescence tracer is analyzed, cleanliness is extremely important. All the beakers and airway models must be kept away from the source of aerosol. Cover them with lint-free tissue papers and keep them in a closed cabinet. Rinse them thoroughly with purified water before use.

4. PROCEDURE

4.1 Aerosol Sampling

1. Generate test aerosols and check the particle size with OPC or APS (see Appendix).
2. Load a filter in each filter holder and connect the filter holders to the outlets of the airway model.
3. Connect the inlet of the model to an aerosol sampling tube.
4. Position the model downward and secure the filter holders with three-prong clamps.

5. Set the timer and alarm for a desired sampling time, turn on the vacuum pump, quickly adjust sampling flow rates by turning the valves in the rotameters, and start the timer.
6. During sampling, check the particle size of aerosol every 5 min using OPC or APS.
7. After sampling, turn off the vacuum pump, disconnect the airway model from the sampling tube, and separate the filter holders from the model.

4.2 Sample Analysis

1. Remove filters from filter holders, place each filter in a 100 ml beaker, and keep the beakers inside a sealed container.
2. Keep filter connectors in a clean container and cover them with lint-free tissue papers.
3. Position the airway model vertically on a laboratory stand and connect a funnel to the outlet of the model via Tygon tubing.
4. Lower the funnel to a level below the outlet of the model and pour ten ml of purified deionized water into the funnel little by little. While pouring, shake the funnel and connecting tubing intermittently to remove air bubbles.

WARNING: Make sure that water does not run up into the model.

5. Raise the funnel slowly until water rises to a premarked levels in the model. Hold the funnel still for a few seconds there and lower the funnel to the starting level. Repeat this five times and pour the water into a 50 ml beaker.
6. Repeat step 5 for all other premarked levels in the model.
7. Remove the beakers containing sample filters from the container and pour 50 ml of purified deionized water into each beaker. Make sure that filters are completely immersed in the water. Sonicate them for two minutes while agitating the water with a glass rod every 30 sec.
8. Analyze each solution with a Turner 112 fluorometer. Select the sensitivity scale of the fluorometer such that the lowest reading among samples does not fall below a 10% level of the full scale. Use the same scale for all samples. This may require additional dilutions for some of the solutions with high concentration.
9. After having analyzed all the samples, rinse the model with isopropyl alcohol and subsequently with clean water: hold the model vertically with one hand, fill the model with alcohol and then quickly evacuate the alcohol.
10. Repeat this three times with alcohol and also with water. Then dry the model by passing filtered dry air through the model.
11. Wrap the model with lint-free tissue paper and store it in a closed container.
12. Clean all the beakers with alcohol and with water and put them in a beaker rack for natural drying.
13. Rinse funnels and funnel tubing with alcohol and water and dry them by blowing dry air.

4.3 Quality Control

Instruments and equipments used for these procedures, including aerosol generator and fluorometer, are covered by separate OPs.

4.4 Evaluation Criteria

All experimental data are plotted against theoretical predictions or estimates based on previous studies. Collected data, when plotted against Stokes number, should fall along

a single trend curve within $\pm 25\%$ deviation from the mean.

4.5 Corrective Action

Suspect or unanticipated results must be evaluated in light of repeat studies.

4.6 Calculation

For comparison, express fluorescence readings of all samples with respect to a 10 ml undiluted volume. Deposition efficiency (DE) in each section of the airway model is then determined by the following equation:

$$DE = (M_{in} - M_{out}) / M_{in}$$

where M_{in} and M_{out} is the mass of fluorescence entering and exiting a given section, respectively. The quantity, $(M_{in} - M_{out})$, is equivalent to the deposited amount of aerosol in the section and is represented by fluorometer readings of the sample from the section. The value of M_{in} is obtained by adding up all the fluorometer readings from the section of interest and those in the downstream.

4.7 Record Keeping

Daily data are recorded chronically in a laboratory notebook. Raw data are also entered into the computerized data sheet, saved in a hard disk driver and electronically transferred to the principal investigator. A copy of the computer data file is also kept in a floppy diskette in the laboratory and a separate copy in the PI's office. Printouts of all the computer data sheet are given to the principal investigator. Copies of data analysis and finished sets are maintained by the PI.

5. APPENDICES

Appendix A: Operating procedure of Turner 112 Fluorometer

APPENDIX A

OPERATING PROCEDURE OF TURNER 112 FLUOROMETER

1. SCOPE OF APPLICATION

This procedure is intended to be a quick guide for operating Turner 112 fluorometer. Detailed procedures must be found in the manufacturer's operating manual.

2. PREREQUISITES

2.1 Equipment and Supplies

Fluorometer (model 112, Sequoia-Turner Corp.)
Cuvette and cuvette holder
Lint-free tissue paper
Purified water

2.2 Training

In-house training by a supervisor is necessary.

3. CAUTIONARY NOTES OR SPECIAL CONSIDERATIONS

Because fluorescence is ubiquitous in the laboratory, an extreme caution must be paid to minimize contamination of samples and supplies as well as equipment.

The instrument contains a high voltage power supply. Do not remove the cover. Refer all servicing to an authorized electrician.

4. PROCEDURE

4.1 General Procedure

1. Turn on power switch
2. Momentarily press lamp start switch and release. Confirm lamp ignition by observing blue glow in lamp indicator.

WARNING: Never observe any lamp without eye protection from ultraviolet radiation. Irreversible damage to vision will result. If accidentally exposed, consult a physician immediately.

3. Repeat Step 2 if lamp does not start
4. Allow 15 minutes for warm-up
5. Set the mode switch to end point mode.
6. Press lever on sample compartment door handle and pull door open. Insert a blank solution in the cuvette holder.

NOTE: Use polyethylene or borosilicate glassware to store samples. Avoid plastics and rubber because the plasticizers in those materials are a frequent source of contamination.

NOTE: It is important to use a set of matching cuvette of which fluorescence responses are comparable with each other within ± 1 instrument reading.

7. Adjust the range selector to 1X or an appropriate range and close the sample compartment door.
8. Adjust the coarse blank knob until Display is in the range of -01.0 to +01.0 and the QA lamp is lit.
9. Adjust the fine blank knob until the display reads 00.0 ± 00.2 . Instrument is now zeroed.
10. Remove the blank cuvette and insert a sample cuvette and close the door.
11. Observe the display panel. When QA lamp comes on, record the reading.

NOTE: It is necessary to readjust the blank value when the range selector is changed.

4.2 Quality Control and Evaluation Criteria

If the sample readings fall below 10, increase the sensitivity (3X, 10X, or 30X) to have the readings above 10. If the results are suspected, repeat Steps 8 to 11.

4.3 Calculation

Fluorescence values in the unknown samples are determined by the following relationship:

$$C_u = (C_s / F_s) F_u$$

- Where C_u = concentration of unknown sample
- C_s = concentration of standard
- F_s = fluorescence reading of standard
- F_u = fluorescence reading of unknown sample

5. PERTINENT REFERENCES

Manufacturer's operating manual must be used for further details.

CRB-604

STANDARD/RECOMMENDED OPERATING PROCEDURE FOR
Inhalation & Analysis of Manual Dispense Aerosols
SOP No. NHEERL-H-HSD-CRB-CSK/95-604-000

This Standard Operating Procedure has been prepared for the sole use of the National Health & Environmental Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, and may not be specifically applicable to the activities of other organizations.

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^c Signature documents the review if no revisions are required.

INHALATION AND ANALYSIS OF MONODISPERSE AEROSOLS FOR LUNG DEPOSITION STUDIES IN HUMANS

S.C. Hu/Chong Kim, July 5, 1995

1 SCOPE OF APPLICATION

This operating procedure is to be followed unless specific deviations are detailed in the protocol for an individual experiment.

2 PREREQUISITES

2.1 Equipment

- Laser aerosol photometer
- Breathing bag inhalation system
- MAGE aerosol generator
- Aerodynamic particle sizer (model 3310B, TSI, Inc.)
- Aerosol diluter
- Signal conditioning box
- Keithley 427 current amplifier
- H.V. power supply for PMT (model 3002D, Canberra Industries, Inc.)
- Personal computer and data acquisition system
- Laser power supply (Melles Groit Corp.)
- Three-way valve and pneumatic valve controller (Hans Rudolf Corp.)
- Solenoid valve power supply

2.2 Supplies and Reagents

- Sebacic Acid (di 2-ethylhexyl ester)
- Sodium Chloride solution (10 mg NaCl/L H₂O)
- Nitrogen
- Compressed air
- Nose clip
- Mouthpiece
- Cleaning alcohol

3 PROCEDURE

3.1 Getting Started

NOTE: If timer is not used to turn on the MAGE, skip steps 5. and 6.

3.1.1 One day prior to use

1. Connect the aerosol breathing bag system to laser aerosol photometer inhalation system.
2. Connect nitrogen supply lines to the pneumatic three-way valve.
3. Wrap and connect heating wires between pneumotachograph and pneumatic three-way valve.
4. Turn the signal conditioning box power on, 12 hours prior to use.

WARNING: It is important to leave the signal conditioning box power on at least over night to achieve a thermal stabilization and to avoid a drifting of base line signals for flow and particle concentration.

5. Setup timer:
 - a) Move the "manual-lever" switch to "off" position.
 - b) Set timer to current date and time.
 - c) Set "on" and "off" trippers on the edge of clock-dial to the desired operation time.
6. Prepare MAGE to be turned on by timer:
 - a) Connect the Collision atomizer to MAGE.
 - b) Close the nuclei bypass valve which is located at MAGE control panel.
 - c) Turn on the compressed nitrogen gas at 20 psig for 5 minutes and then **turn off**.
 - d) Switch the mains, reheater and temperature controller power switches to "on" position.

NOTE: Make sure all the instrument settings are on default positions shown in Appendix A.

3.1.2 Warming up

7. Turn MAGE system on (refer to Appendix C, MAGE), 1.5 hours prior to use.
8. Turn laser power switch on, half hour prior to use.
9. Turn H.V. power supply on, half hour prior to use.
10. Turn Keithley current amplifier power switch on, half hour prior to use.
 - a) Set gain at "zero check".
 - b) If light on "overload" is on, use small screw driver adjust at "zero adj" until light is off.
 - c) Set gain back to 10^5 .
11. Turn pneumatic valve power switch on.
12. Turn solenoid valve power switch on.
13. Turn the Aerodynamic Particle Sizer on (refer to Appendix D, APS), half hour prior to use.

3.1.3 Loading software and calibrating flow rate

14. Turn main computer and monitor power switches on.
15. Create a new subdirectory D:\1##\, where ## is the subject's two digit ID number, to store the experimental data of this subject: Type "D:" <Enter>, "md 1##" <Enter>.

NOTE: A complete file naming strategy is given in Appendix B

16. Type "GO" <Enter> to install "BOLUS.2" program.

NOTE: It takes about 1 minute to completely load the "BOLUS.2" program, then the menu "MAIN MENU" is displayed on screen.

17. Calibrate pneumotachograph-flow system:
 - a) Balance the pneumotachograph-flow system at signal conditioning box.
 - b) Install the calibrated rotameter (Fischer & Porter, ser.#7007A4267A1) to the position between compressed air three-way valve and inhalation brass mouth piece.
 - c) Switch the three way valve to the "calibration" side.
 - d) Choose "CALIBRATION: Flow" from menu MAIN MENU.
 - e) Choose "Perform Calibration" from menu FLOW CALIBRATION EQUATION.
 - f) Choose "By Multiple Flows" from menu FLOW CALIBRATION EXPERIMENT.
 - g) Follow the screen instruction to calibrate flow from 0 to 60 lmp by every 10 lmp.

- h) Choose "View Results" from menu FLOW CALIBRATION EXPERIMENT to see the calibration results.
 - i) Press <Esc> or choose "EXIT" from menu to return to menu MAIN MENU.
18. Calibrate integrator-volume system:
- a) Balance the pneumotachograph-flow system at signal conditioning box.
 - b) Choose "CALIBRATION: Volume" from menu MAIN MENU.
 - c) Choose "Perform Calibration" from menu VOLUME CALIBRATION EQUATION.
 - d) Choose "By Flow" from menu FLOW CALIBRATION EXPERIMENT.
 - e) Set flow rate at range 1.5 - 1.8 Volt (about 15 lpm).
 - f) Follow the screen instruction to calibrate volume.
 - g) Choose "View Results" from menu VOLUME CALIBRATION EXPERIMENT to see the calibration results.
 - h) Press <Esc> or choose "EXIT" from menu to return to menu MAIN MENU.
19. Enter subject information:
- a) Choose "Subject Data" from menu MAIN MENU.
 - b) Move pointer to "Subject ID#", press <Enter>, type subject's two digital ID number ## and press <Enter>.
 - c) Move pointer to "Visit number", press <Enter>, type the visit number # and press <Enter>.
 - d) Press <Esc> or choose "EXIT" from menu to return to menu MAIN MENU.
20. Enter experimental parameters:
- a) Choose "Manoeuvre Data" from menu MAIN MENU.
 - b) Choose "Experimental Method" from menu and select the method.
 - c) Choose "Particle Size" from menu and select the particle size.
 - d) Choose "Tidal Volume" from menu and select the tidal volume.
 - e) Choose "Inspiratory Flow Rate" from menu and select the volumetric flow.
 - f) Choose "Expiratory Flow Rate" from menu and select the volumetric flow.
 - g) Choose "Bolus Penetration Volume" from menu and select single or continuous breathing maneuver.
 - h) Press <Esc> or choose "EXIT" from menu to return to menu MAIN MENU.
 - i) Press <Esc> or choose "EXIT" from menu MAIN MENU to exit menu environment.
- The system is now on stand by for the experiment now.

NOTE: Steps 19 and 20 are the necessary procedures to arrange the data file in order to save experimental data or to retrieve data from hard disk.

3.2 Aerosol Inhalation Experiment

Important Functional Keys:

1. Press <F1> to have instruction menu.
2. Press <F4> to perform aerosol inhalation experiment.
3. Press <Shft-F3> to view aerosol concentration vs. respiratory flow plot.
4. Press <F6> to calculate results.
5. Press <F10> to save experimental raw data.

NOTE: To run experiments at the same condition, repeat steps 2-5.

6. Press <F2> to change experimental parameters.
7. Press <F3> to change parameters for data acquisition system.

APPENDICES

- Appendix A Instrument Default Settings
- Appendix B Raw Data File Naming Strategies
- Appendix C Operating Procedure for MAGE Generator To Generate DES Monodisperse Aerosols
- Appendix D Operation Of Aerodynamic Particle Sizer and Aerosol Diluter

APPENDIX A

INSTRUMENTS DEFAULT SETTINGS

1. KEITHLEY 427 CURRENT AMPLIFIER

Gain: 10^5
Suppression: off
Rise time: 30 msec

2. H.V. POWER SUPPLY (MODEL 3002D) FOR PMT

-850 V

3. SIGNAL CONDITIONING BOX

Flow and volume switches: "inverted" (down side)
Reset switch: "computer"
Solenoid switch: "normally off"
Flow gain: 5.20
Volume gain: 7.75
Temperature controller:
 Sensor type: Pt type (function .16, 9.16)
 Temperature: 40°C

4. MAGE

Heating coil power controller: 55
Reheater temperature controller:
 Sensor type: N type (function .16, 3.16)
 Temperature: 320°C for $5\ \mu\text{m}$
 Temperature: 280°C for 1 and $3\ \mu\text{m}$
Atomizer solution: 10 mg NaCl / liter H_2O (0.001%) for $D_p = 1$ and $3\ \mu\text{m}$
Atomizer solution: 5 mg NaCl / liter H_2O (0.0005%) for $D_p = 5\ \mu\text{m}$
Atomizer pressure (N_2): 20 psig
Boiler temperature settings:
 $D_p = 1\ \mu\text{m}$: 170°C
 $D_p = 3\ \mu\text{m}$: 220°C
 $D_p = 5\ \mu\text{m}$: 245°C

APPENDIX B

RAW DATA FILE NAMING STRATEGIES

The experimental raw (digital) data is stored by ASYST data format in file d:\1##\Abcdefgh.##v.

Filename: d:\1##\Abcdefgh.##v

- d: disk D
- ##: subject's two digital ID number
- v: subject's visit number
- A: project name, Adeposit
- b: experimental method:
 - N: baseline study
 - a, b, c,: 0, 15, 30, ... minutes post methacholine change
 - 1, 2, 3,: 0, 15, 30, ... minutes post histamine change
- c: particle size:
 - 1= 1 μm
 - 3= 3 μm
 - 5= 5 μm
- d: tidal volume:
 - 1= 500 ml
 - 2= 1 liter
 - 3= 1.5 liter
- e: inspiratory flow rate:
 - 1= 150 ml/s
 - 2= 250 ml/s
 - 3= 500 ml/s
 - 4= 1 l/s
- f: expiratory flow rate:
 - 1= 150 ml/s
 - 2= 250 ml/s
 - 3= 500 ml/s
 - 4= 1 l/s
- g: penetration volume:
 - 1= 100 ml
 - 2= 150 ml
 - 3= 200 ml
 - 4= 250 ml
 - 5= 300 ml
 - 6= 500 ml
- h: experiment number:
 - 1, 2, 3,, 0: repeated measurement 1, 2, 3,, 10

APPENDIX C

OPERATING PROCEDURE FOR MAGE GENERATOR TO GENERATE DES MONODISPERSE AEROSOLS

PRELIMINARY

1. Check the silica gel color.
2. Check the level of DEHS oil in the boiler.

USE

NOTE: If MAGE is turned on by timer, skip steps 2, 3, and 9.

1. Fill atomizer solution to 2/3 depth of the Collison flash.
2. Connect the Collison atomizer to MAGE.
3. Close the nuclei bypass valve which is located at MAGE control panel.
4. Turn on the compressed nitrogen and set to the desired pressure (20 psig).
5. Completely open the exhaust valve which connects dilution tube and exhaust duct.
6. Completely open the pressure controlling clamp which is located between aerosol reservoir and oil trap bottle.
7. Turn on the dilution air to approximate 50 lpm.
8. Set the boiler temperature to the desired value (refer to Appendix A).
9. Turn the mains, reheater and temperature controller power switches on.
10. Turn heating coil power controller on.
11. Wait for 1.5 hours to stabilize the system.
12. Fine tuning the particle size by means of regulating atomizer pressure and nuclei flow.

NOTE: If aerosol is not monodispersed, it could be improved by adjusting the reheater temperature.

After Use

1. Open the nuclei bypass valve completely.
2. Completely open the exhaust valve.
3. Completely open the pressure controlling clamp.
4. Turn off the mains, heating coil power controller, reheater and temperature control power switches.
5. Turn off the compressed nitrogen.
6. Turn off the dilution air.

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APPENDIX D

OPERATION OF AERODYNAMIC PARTICLE SIZER AND AEROSOL DILUTER

WARM-UP

1. Turn on APS main power switch, then the pump and laser.
2. Warm up APS for half hour to stabilize sensor and pump.

FLOW ADJUSTMENT

3. Use the "total-flow" potentiometer to adjust the nozzle ΔP to the value on the data sheet (2.884 volt).
4. Adjust the voltage of the "sheath-air" using the sheath-air valve until the voltage display for shear-air is within ± 1 millivolt of the value on the data sheet (4.382 Volt).

SOFTWARE

5. Turn APS computer and monitor power switches on, and then type "TSI" <Enter> to install APS software. After APS software is installed completely, main menu screen is displayed on the monitor.

- **To return to the previous submenu, press <Esc>.
- **To use the default settings of parameters, skip step 6.

6. To change the setting of parameters: in main menu screen, choose "Main menu", and then "Parameters".

Default settings:

- particle density: 0.91 (DEHS)
- dilution ratio: 1:1
- efficiency correction: D1
- background subtraction: off
- density correction: on

7. To start sampling: in main menu screen, choose "Run menu", and then "Auto run".
8. To view statistics results from screen: in main menu screen, choose "Run menu", and then "Statistics".
9. To print statistics results from printer: in main menu screen, choose "Run menu", and then "Print statistics".
10. To Print graph results from printer: in main menu screen, choose "Run menu", and then "Print screen".
11. To unload APS software: in main menu screen, choose "Termination menu", and then "Terminate program".

AFTER USE

12. Follow step 11 to unload APS software.
13. Turn off APS computer and monitor.
14. Turn off APS laser power switch, pump power switch, and then main power switch.

AEROSOL DILUTER

If the aerosol concentration is too high, use APS with a diluter to reduce the concentration and to minimize the coincidence loss of particles.

1. Remove the diluter cover for easy positioning.
2. Remove the red cap from the nozzle inlet of diluter.
3. Remove the aerosol inlet assembly (a T-connector and a cartridge filter) from the APS inlet and install it to the diluter inlet.
4. Slide the APS mounting ring over the APS inlet so that it sits flat on the top of the APS cabinet.
5. Carefully position the diluter on the top of APS over the mounting ring so that the outlet of the diluter aligns perfectly with the mounting ring and APS inlet tube.
6. Correct the dilution ratio in the APS software by following step 6 described above.

STANDARD/RECOMMENDED OPERATING PROCEDURE FOR
Bolus Aerosol Inhalation & Analysis
SOP No. NHEERL-H-HSD-CRB-CSK/95-605⁰⁰⁰

This Standard Operating Procedure has been prepared for the sole use of the National Health & Environmental Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, and may not be specifically applicable to the activities of other organizations.

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(SUPERVISOR INITIAL THOSE REQUIRED)

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^c Signature documents the review if no revisions are required.

BOLUS AEROSOL INHALATION AND ANALYSIS

S. C. Hu/Chong Kim, July 5, 1995

1 SCOPE OF APPLICATION

This procedure will allow to perform bolus aerosol inhalation test in humans and subsequent analysis of data.

2 PREREQUISITES**2.1 Equipment**

Laser aerosol photometer
Laser power supply (Melles Griot Corp.)
Bolus injection system
MAGE aerosol generator
Aerodynamic particle sizer (model 3310B, TSI Inc., St Paul, MN)
Aerosol diluter
Signal conditioning box
Keithley 427 current amplifier
H.V. power supply for PMT (model 3002D, Canberra Industries, Inc.)
Pneumatic three-way valve and controller (Hans Rudolf Corp.)
Personal computer and data acquisition system

2.2 Supplies and Reagents

Sebacic Acid (di-2-ethylhexyl ester)
Sodium Chloride solution (10 mg NaCl/L H₂O)
Nitrogen
Compressed air
Nose clip
Mouthpiece
Alcohol

2.3 Training

In-house training is required to familiarize the computerized operation and data acquisition procedures.

3 PROCEDURE**3.1 Getting Started**

**If timer is not used to turn on the MAGE, skip steps 4. and 5.

3.1.1 One day prior to use

1. Connect the aerosol bolus injection system to the aerosol inhalation system, tight two wingnuts.
2. Wrap and connect heating wires between pneumotachograph and bolus injection tube.
3. Turn the signal conditioning box power on, 12 hours prior to use.

WARNING: It is important to leave the signal conditioning box power on at least over night to achieve a thermal stabilization and to avoid a drifting of base line signals for flow and particle concentration.

4. Setup timer:
 - a) Move the "manual-lever" switch to "off" position.
 - b) Set timer to current date and time.
 - c) Set "on" and "off" trippers on the edge of clock-dial to the desired operation time.
5. Prepare MAGE to be turned on by timer:
 - a) Connect the Collision atomizer to MAGE.
 - b) Close the nuclei bypass valve which is located at MAGE control panel.
 - c) Turn on the compressed nitrogen gas at 20 psig for 5 minutes and then **turn off**.
 - d) Switch the mains, reheater and temperature controller power switches to "on" position.

NOTE: Make sure all the instrument settings are on default positions shown in Appendix A.

3.1.2 Warming up

6. Turn MAGE system on (refer to Appendix C, MAGE), 1.5 hours prior to use.
7. Turn laser power switch on, half hour prior to use.
8. Turn H.V. power supply on, half hour prior to use.
9. Turn Keithley current amplifier power switch on, half hour prior to use.
 - a) Set gain at "zero check".
 - b) If light on "overload" is on, use small screw driver adjust at "zero adj" until light is off.
 - c) Set gain back to 10^5 .
10. Turn the Aerodynamic particle sizer on (refer to Appendix D, APS), half hour prior to use.

3.1.3 Loading software and calibrating flow rate

11. Turn main computer and monitor power switches on.
12. Create a new subdirectory D:\1##\, where ## is the subject's two digital ID number, to store the experimental data of this subject: Type "D:" <Enter>, "md 1##" <Enter>.

NOTE: A complete file naming strategy is given in Appendix B.

13. Type "GO" <Enter> to install "BOLUS.2" program.

NOTE: It takes about 1 minute to completely load the "BOLUS.2" program, then the menu "MAIN MENU" is displayed on screen.

14. Calibrate pneumotachograph-flow system:
 - a) Balance the pneumotachograph-flow system at signal conditioning box.
 - b) Fully open the resistor clamp located between bolus injection block and humidifier reservoir.
 - c) Install the calibrated rotameter (Fischer & Porter, ser.#7007A4267A1) to the position between compressed air three way valve and inhalation brass mouth piece.
 - d) Switch the three way valve to the "calibration" side.
 - e) Choose "CALIBRATION: Flow" from menu MAIN MENU.
 - f) Choose "Perform Calibration" from menu FLOW CALIBRATION EQUATION.
 - g) Choose "By Multiple Flows" from menu FLOW CALIBRATION EXPERIMENT.
 - h) Follow the screen instruction to calibrate flow from 0 to 60 lpm by every 10 lpm.

- l) Choose "View Results" from menu FLOW CALIBRATION EXPERIMENT to see the calibration results.
 - j) Press <Esc> or choose "EXIT" from menu to return to menu MAIN MENU.
15. Calibrate integrator-volume system:
- a) Balance the pneumotachograph-flow system at signal conditioning box.
 - b) Choose "CALIBRATION: Volume" from menu MAIN MENU.
 - c) Choose "Perform Calibration" from menu VOLUME CALIBRATION EQUATION.
 - d) Choose "By Flow" from menu FLOW CALIBRATION EXPERIMENT.
 - e) Set flow rate at range 1.5 - 1.8 Volt (about 15 lpm).
 - f) Follow the screen instruction to calibrate volume.
 - g) Choose "View Results" from menu VOLUME CALIBRATION EXPERIMENT to see the calibration results.
 - h) Press <Esc> or choose "EXIT" from menu to return to menu MAIN MENU.
16. Enter subject information:
- a) Choose "Subject Data" from menu MAIN MENU.
 - b) Move pointer to "Subject ID#", press <Enter>, type subject's two digital ID number ## and press <Enter>.
 - c) Move pointer to "Visit number", press <Enter>, type the visit number # and press <Enter>.
 - d) Press <Esc> or choose "EXIT" from menu to return to menu MAIN MENU.
17. Enter experimental parameters:
- a) Choose "Maneuver Data" from menu MAIN MENU.
 - b) Choose "Experimental Method" from menu and select the method.
 - c) Choose "Particle Size" from menu and select the particle size.
 - d) Choose "Tidal Volume" from menu and select the tidal volume.
 - e) Choose "Inspiratory Flow Rate" from menu and select the volumetric flow.
 - f) Choose "Expiratory Flow Rate" from menu and select the volumetric flow.
 - g) Choose "Bolus Penetration Volume" from menu and select the penetration volume.
 - h) Press <Esc> or choose "EXIT" from menu to return to menu MAIN MENU.
 - i) Press <Esc> or choose "EXIT" from menu MAIN MENU to exit menu environment.
- The system is now on stand by for the experiment now.

NOTE: Steps 16 and 17 are the necessary procedures to arrange the data file in order to save experimental data or to retrieve data from hard disk.

3.2 Bolus Experiment

Important Functional Keys:

1. Press <F1> to have instruction menu.
2. Press <F4> to perform bolus experiment.
3. Press <Shift-F3> to view aerosol vs. respiratory flow bolus plot.
4. Press <F6> to calculate results.
5. Press <F10> to save experimental raw data.

**To run experiments at the same condition, repeat steps 2-5.

6. Press <F2> to change experimental parameters.
7. Press <F3> to change parameters for data acquisition system.

NOTE: Bolus half width is determined by the duration of solenoid valve opening and the injection pressure. Bolus width will be greater with an increase of the duration of valve opening or the injection pressure.

NOTE: Adjusting the offset volume allows a fine tuning of penetration volume. The larger the offset volume is, the earlier the solenoid valve opens. If a subject tends to inhale below a target volume, then increasing the offset volume can compensate for the shallow inhalation and bring penetration volumes closer to the target values.

3.3 After Use

1. Turn off APS system (refer to "after use" at Appendix D, APS).
2. Turn off MAGE system (refer to "after use" at Appendix C, MAGE).

NOTE: Remember to turn off the dilution air and N₂.

3. Turn the signal conditioning box power off.
4. Reset gain of Keithley current amplifier to "zero check".
5. Turn Keithley current amplifier power switch off.
6. Turn H.V. power supply off.
7. Turn laser power switch off.
8. Type "BYE" and press <Enter> to exit ASYST.
9. Turn main computer and monitor power switches off.
10. Turn off the humidified air.
11. Fully open the resistor pinch clamp.
12. Remove the brass mouth piece from the inhalation system and plug the system with stopper.
13. Wash the brass mouth piece with antiseptic/antimicrobial cleanser and water, and then rinse with isopropyl alcohol.
14. Connect brass mouth piece to the aerosol inhalation system

3.4 Quality Control

Default settings of the instruments are described in Appendix A.

Procedures for MAGE, is included in Appendix C.

Procedures for Aerodynamic Particle Sizer and Aerosol Diluter are included in Appendix D.

3.5 Evaluation Criteria

Volumetric half width of the inhaled bolus should be 30 - 50 ml.

3.6 Record Keeping

Experiment raw data are stored in computer hard disk drive. Each filename is identified by subject number and experimental protocol as described in Appendix B. These data must be backed up to the tape after the individual subject completes the study. Calculated aerosol recovery and penetration volume must also be recorded in a notebook.

APPENDICES

- Appendix A Instruments Default Settings
- Appendix B Raw Data File Naming Strategies
- Appendix C Operating Procedure for MAGE Generator To Generate DES Monodisperse Aerosols
- Appendix D Operation Of Aerodynamic Particle Sizer and Aerosol Diluter

APPENDIX A

INSTRUMENTS DEFAULT SETTINGS

1. KEITHLEY 427 CURRENT AMPLIFIER

Gain: 10^5
Suppression: off
Rise time: 30 msec

2. H.V. POWER SUPPLY (MODEL 3002D) FOR PMT

-850 V

3. SIGNAL CONDITIONING BOX

Flow and volume switches: "inverted" (down side)
Reset switch: "computer"
Solenoid switch: "normally off"
Flow gain: 5.20
Volume gain: 7.75
Temperature controller:
 Sensor type: Pt type (function .16, 9.16)
 Temperature: 40°C

4. MAGE

Heating coil power controller: 55
Reheater temperature controller:
 Sensor type: N type (function .16, 3.16)
 Temperature: 320°C for $5\ \mu\text{m}$
 Temperature: 280°C for 1 and $3\ \mu\text{m}$
Atomizer solution: 10 mg NaCl / liter H_2O (0.001%) for $D_p = 1$ and $3\ \mu\text{m}$
Atomizer solution: 5 mg NaCl / liter H_2O (0.0005%) for $D_p = 5\ \mu\text{m}$
Atomizer pressure (N_2): 20 psig
Boiler temperature settings:
 $D_p = 1\ \mu\text{m}$: 170°C
 $D_p = 3\ \mu\text{m}$: 220°C
 $D_p = 5\ \mu\text{m}$: 245°C

APPENDIX B

RAW DATA FILE NAMING STRATEGIES

The experimental raw (digital) data is stored by ASYST data format in file d:\1##\Abcdefgh.##v.

Filename: d:\1##\Abcdefgh.##v

- d: disk D
- ##: subject's two digital ID number
- v: subject's visit number
- A: project name, Adeposit
- b: experimental method:
 - N: baseline study
 - a, b, c, ...: 0, 15, 30, ... minutes post methacholine change
 - 1, 2, 3, ...: 0, 15, 30, ... minutes post histamine change
- c: particle size:
 - 1= 1 μm
 - 3= 3 μm
 - 5= 5 μm
- d: tidal volume:
 - 1= 500 ml
 - 2= 1 liter
 - 3= 1.5 liter
- e: inspiratory flow rate:
 - 1= 150 ml/s
 - 2= 250 ml/s
 - 3= 500 ml/s
 - 4= 1 l/s
- f: expiratory flow rate:
 - 1= 150 ml/s
 - 2= 250 ml/s
 - 3= 500 ml/s
 - 4= 1 l/s
- g: penetration volume:
 - 1= 100 ml
 - 2= 150 ml
 - 3= 200 ml
 - 4= 250 ml
 - 5= 300 ml
 - 6= 500 ml
- h: experiment number:
 - 1, 2, 3, ..., 0: repeated measurement 1, 2, 3, ..., 10

APPENDIX C

OPERATING PROCEDURE FOR MAGE GENERATOR TO GENERATE DES MONODISPERSE AEROSOLS

PRELIMINARY

1. Check the silica gel color.
2. Check the level of DEHS oil in the boiler.

USE

NOTE: If MAGE is turned on by timer, skip steps 2, 3, and 9.

1. Fill atomizer solution to 2/3 depth of the Collision flash.
2. Connect the Collision atomizer to MAGE.
3. Close the nuclei bypass valve which is located at MAGE control panel.
4. Turn on the compressed nitrogen and set to the desired pressure (20 psig).
5. Completely open the exhaust valve which connects dilution tube and exhaust duct.
6. Completely open the pressure controlling clamp which is located between aerosol reservoir and oil trap bottle.
7. Turn on the dilution air to approximate 50 lpm.
8. Set the boiler temperature to the desired value (refer to Appendix A).
9. Turn the mains, reheater and temperature controller power switches on.
10. Turn heating coil power controller on.
11. Wait for 1.5 hours to stabilize the system.
12. Fine tuning the particle size by means of regulating atomizer pressure and nuclei flow.

NOTE: If aerosol is not monodispersed, it could be improved by adjusting the reheater temperature.

After Use

1. Open the nuclei bypass valve completely.
2. Completely open the exhaust valve.
3. Completely open the pressure controlling clamp.
4. Turn off the mains, heating coil power controller, reheater and temperature control power switches.
5. Turn off the compressed nitrogen.
6. Turn off the dilution air.

APPENDIX D

OPERATION OF AERODYNAMIC PARTICLE SIZER AND AEROSOL DILUTER

WARM-UP

1. Turn on APS main power switch, then the pump and laser.
2. Warm up APS for half hour to stabilize sensor and pump.

FLOW ADJUSTMENT

3. Use the "total-flow" potentiometer to adjust the nozzle ΔP to the value on the data sheet (2.884 volt).
4. Adjust the voltage of the "sheath-air" using the sheath-air valve until the voltage display for shear-air is within ± 1 millivolt of the value on the data sheet (4.382 Volt).

SOFTWARE

5. Turn APS computer and monitor power switches on, and then type "TSI" <Enter> to install APS software. After APS software is installed completely, main menu screen is displayed on the monitor.

**To return to the previous submenu, press <Esc>.

**To use the default settings of parameters, skip step 6.

6. To change the setting of parameters: in main menu screen, choose "Main menu", and then "Parameters".

Default settings:

particle density: 0.91 (DEHS)
dilution ratio: 1:1
efficiency correction: D1
background subtraction: off
density correction: on

7. To start sampling: in main menu screen, choose "Run menu", and then "Auto run".
8. To view statistics results from screen: in main menu screen, choose "Run menu", and then "Statistics".
9. To print statistics results from printer: in main menu screen, choose "Run menu", and then "Print statistics".
10. To Print graph results from printer: in main menu screen, choose "Run menu", and then "Print screen".
11. To unload APS software: in main menu screen, choose "Termination menu", and then "Terminate program".

AFTER USE

12. Follow step 11 to unload APS software.
13. Turn off APS computer and monitor.
14. Turn off APS laser power switch, pump power switch, and then main power switch.

AEROSOL DILUTER

If the aerosol concentration is too high, use APS with a diluter to reduce the concentration and to minimize the coincidence loss of particles.

1. Remove the diluter cover for easy positioning.
2. Remove the red cap from the nozzle inlet of diluter.
3. Remove the aerosol inlet assembly (a T-connector and a cartridge filter) from the APS inlet and install it to the diluter inlet.
4. Slide the APS mounting ring over the APS inlet so that it sits flat on the top of the APS cabinet.
5. Carefully position the diluter on the top of APS over the mounting ring so that the outlet of the diluter aligns perfectly with the mounting ring and APS inlet tube.
6. Correct the dilution ratio in the APS software by following step 6 described above.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
RESEARCH TRIANGLE PARK, NC 27711

April 4, 2002

MEMORANDUM

SUBJECT: Exposure of Subjects to Sebacate Particles in ADEPOSIT

FROM: Robert Devlin, Chief *R Devlin*
Clinical Research Branch

TO: John Vandenberg, Acting Director
Human Studies Division

Dr. Kim was asked to calculate the maximum dose of 5 micron particles delivered to each of the subjects in his study. His calculations are appended to this letter as "Estimation of maximum dose of ADEPOSIT subjects." The maximum dose varied from 0.89 – 2.69 mg. To validate the approach taken by Dr. Kim in arriving at these calculations, two outside dosimetry experts from CIIT were asked to perform an independent analysis on data provided for two subjects, who represent a "typical" subject and one with the greatest potential risk for adverse effects as a result of exposure to airborne materials (a subject with COPD). The calculations were carried out using the model of Anjilvel and Asgharian (1995) and attached to this letter as "Assessment of Potential Maximum Dose in ADEPOSIT Subjects." Their report concludes that the approach taken by Dr. Kim was valid.

—Note that three different size particles were used in this study. These calculations were performed on exposures in which the largest size particles (5 microns) were used, since that would result in the largest mass of particles delivered to the lung. However, some subjects were exposed to 3 micron and 1 micron particles, in addition to 5 micron particles. These exposures were separated by a few days or up to a few weeks. Taking into account clearance of particles after each exposure, Dr. Kim has calculated that the additional particle dose delivered to these subjects may be estimated by multiplying the dose received with 5 micron particles by 1.3. A copy of his e mail explaining these calculations is appended to this letter.

Dr. Bennett, a researcher at UNC who is an expert in human dosimetry, was asked to compare the dose received by Dr. Kim's subjects to that received by humans in other dosimetry studies. After reading several papers in which humans were exposed to the same kind of particles as used in Dr. Kim's study, Dr. Bennett was unable to make a direct comparison – primarily because the papers did not contain sufficient details (such as the number of breaths of particles each subject

Enclosure (j)

inhaled) to allow a calculation of total dose delivered. However, he was able to calculate the concentration of 1, 3, 5 micron particles used in those studies. One such paper is attached to this letter (Brand et al., 1999). In this paper subjects were exposed to a particle concentration of 260 mg/m³ and there were no reported adverse health effects associated with the study. Dr. Kim's subjects were exposed to a maximum particle concentration of 150 mg/m³ with no reported adverse health effects. Assuming subjects in both studies were using the same breathing pattern, Dr. Kim's subjects inhaled only 58% as much particle mass as the subjects in the Brand study.

Estimation of maximum dose of ADEPOSIT subjects

In ADEPOSIT study, deposition fraction of inhaled inert oil aerosols (1, 3 and 5 μm diameter) is measured *in situ* in volunteer subjects. Subjects visit the lab three times on different days and DF is measured for one size aerosol in each visit. On a study day, subjects inhale a test aerosol up to 12 breaths with a predetermined breathing pattern, and the same procedure is repeated with six to twelve different breathing patterns. Therefore, the subject may inhale the aerosol up to 144 breaths. The actual lung deposition dose may be assessed by the following relationship:

$$D_i = C_i \cdot V_i \cdot DF_i \quad \text{for each breath}$$

$$D = C \cdot V \cdot DF \cdot N \quad \text{for total}$$

where D_i = deposition dose for *i*-th breath

C_i = concentration of inhaled aerosol for a given breath ($\mu\text{g}/\text{liter}$)

V_i = tidal volume, volume of *i*-th breath (liter)

DF_i = deposition fraction of *i*-th breath ($DF = 1 - \text{exhaled/inhaled}$)

D = total deposition dose for all breath (μg)

N = total number of breaths inhaled

C, V, DF = average of all breaths

Here, D_i varies breath by breath because the subject cannot maintain the exact same breath during inhalation. D_i and N also vary for different subjects. Tracking down the breath by breath variation of these values is practically impossible. However, the values can be averaged over a number of breaths and the total number of breaths inhaled may be estimated from the average data. During the study, C_i is not measured, but monitored by an electric signal. The default value is about 6 volt that corresponds to about 50 $\mu\text{g}/\text{l}$ concentration for 5 μm aerosol. Dose estimation is attempted for 5 μm aerosol only because the dose of smaller size particles is much smaller. The summary of individual dose estimation is given in the Table.

Maximum dose estimation for ADEPOSIT subjects

Normal subjects		Elderly subjects		Asthmatic subjects		COPD subjects	
Subj #	Dose (mg)	Subj #	Dose (mg)	Subj #	Dose (mg)	Subj #	Dose (mg)
N01	1.78	E03	1.90	A01	1.20	C01	2.64
N02*	1.00	E04	1.69	A02	1.10	C02	2.25
N03	1.91	E05	1.86	A03	1.17	C03	2.55
N05	2.15	E06	1.63	A04	1.06	C04	2.69
N06	1.91	E07	1.52	A05	1.04	C05	2.39
N08	1.87	E08	1.76	A06	0.89	C06	2.17
N09	2.28	E09	1.51	A07	0.97		
N11	2.23	E10	1.47	A08	1.94		
N12	2.27	E11	2.10	A09	2.40		
N13	2.04	E12	1.61	A10	2.15		
N14	2.00	E13	2.06	A11	2.17		
N15	2.08	E14	1.93	A12	2.19		
N17	2.13	E15	2.02	A13*	0.70		
		E16	1.65	A14*	0.10		
		E17	1.93	A15	2.29		
		E18	1.76	A16	2.22		
		E19	2.13	A17*	0.72		
				A19	2.24		
				A20	2.16		
				A21	1.85		
Highest	2.28		2.13		2.40		2.69
Lowest	1.00		1.51		0.10		2.17
Mean	1.97		1.79		1.53		2.45

* Partial study

CONFIDENTIAL

Assessment of Potential Maximum Dose in ADEPOSIT Subjects

Submitted to

Dr. James Samet
U. S. Environmental Protection Agency
58 D U.S. EPA Mailroom, Research Triangle Park, NC

Submitted by

CIIT Centers for Health Research
6 Davis Dr., Research Triangle Park, NC

Bahman Asgharian, Ph.D.
Analysis Team Leader

Date

Fred J. Miller, Ph.D.

Date

Vice President for Research

Objective

An independent study was conducted at CIIT Centers for Health Research to assess the dose received by 2 subjects (A21 & C05) in the protocol IRB#91-EPA 226 during a brief exposure to di (2-ethylhexyl) sebacate (DEHS) particles. These subjects corresponded to typical cases among asthmatic and chronic obstructive pulmonary disease (COPD) patient groups with the greatest potential risk for adverse effects as a result of exposure to the airborne materials.

Approach

The deposition calculations were carried out using the multiple-path lung deposition model of Anjilvel and Asgharian (1995). There are no lung morphometry measurements currently available on individuals with asthma or COPD. For the current analyses, the lung geometry of normal, healthy adults was used in the calculations since study subjects were only mildly diseased. Two adult human lung geometries with asymmetric branching structures in the tracheobronchial region (TB) were generated. The generated lung structures were based on the morphometric measurements of Raabe et al. (1976). Each lung consisted of a stochastically generated asymmetric branching structure in the TB region (Koblinger and Hofmann, 1990; Asgharian et al., 2001) completed by attaching an 8-generation symmetrical acinus (Yeh et al., 1979) to the end of the terminal bronchioles. These two lungs were selected from a pool of 30 stochastically generated lungs and represented limiting cases of the lungs with the smallest and largest number of TB airways. Incorporating the asymmetric feature of the lung structure allowed for more realistic assessment of the site-specific and local deposition of particles in the respiratory tract.

Subject Input Data

Various inputs such as the subject's lung parameters (e.g. functional residual capacity, head volume etc.) and breathing parameters (tidal volume, and breathing frequency) were necessary to perform the calculations. To obtain these data and to ensure that CIIT understood the manner in which Dr. Kim's study was conducted, a meeting was held with Drs. C. S. Kim, J. Samet, and B. Asgharian on Monday, March 4, 2002. The exposure

data and other necessary information were obtained to enable the CIIT team to calculate the dose received by these 2 individuals.

Dr. Kim stated that these 2 subjects were exposed orally for one day only to 5 μ m-diameter monodisperse particles of mass density 0.89 g/cm³ at a concentration of 50 mg/m³. The subjects did not return for any additional exposures. The highest dose to an individual was therefore at the end of the exposure day when there was no appreciable clearance. The results calculated in the report were thus limited to the deposition mass only. The breathing parameters and the exposure concentrations were identical for the 2 subjects. Each subject was trained to inhale 4 different volumes of air at various breathing flow rates. The breathing frequencies were calculated and are provided in Table 1 along with the tidal volumes for each exposure scenario. While we used the functional residual capacity (FRC) values supplied by Dr. Kim, the value for FRC of 6.91 liters for subject C05 is, in our opinion, highly suspect for an individual with mild COPD and should be verified by Dr. Kim.

Each subject was exposed to 11 different breathing scenarios on the exposure day. The number of breaths varied for each exposure scenario. The information on the number of breath per exposure scenario was provided by Dr. Kim for one individual (A21) and an estimate was given for the other subject (C05). Due to lack of information, it was assumed that the inhalation and exhalation times were equal and there was no pause between inhalation and exhalation. Default parameter values available in the literature were used when the values were missing.

Deposition fraction during one breathing cycle via mouth breathing was calculated for the two lung geometries using the FRC, breathing and lung parameters of the subjects, and particle size characteristics. Total and regional mass deposited in the respiratory tract in the subjects was subsequently calculated for each breathing scenario from the expression given below.

$$\text{Mass Deposited} = \text{Deposition Fraction} \times \text{Exposure Concentration} \times \text{Tidal Volume} \times \text{Number of Breaths}$$

The calculated deposition fraction in each region of the lung was substituted in the above equation to obtain the corresponding deposited mass.

Results

Tables 2–5 show the head, TB, pulmonary (PUL), and total deposition results in the 2 lung geometries for each breathing scenario. Accumulated mass deposited in each subject at the end of the day from inhaling the particles in various exposure scenarios is given in the last row of each table. Tables 2 and 3 give the calculated data for subject A21, while the data for subject C05 is given in Tables 4 and 5.

Despite oral breathing, a significant portion of the particles were removed from the inhaled air before reaching the lower respiratory tract. Nonetheless, deposition in the lower respiratory tract was significant. Patient A21, having a smaller FRC of almost half that of patient C05, showed a larger deposition fraction of the inhaled materials. The total deposition fraction varied between 80 to 98% for this patient. The mass amount of the total deposited material is similar for the 2 subjects (2.8 mg for A21 versus 2.5 mg for C05 where the values are the calculated average deposition in the 2 stochastic lungs). The amount deposited in the lower respiratory tract is larger for subject A21 (averages of 1.9 mg for A21 versus 1.3 mg for C05). This difference and the fact that patient A21 had a smaller FRC (and thus smaller lung) are probably why the deposited mass per unit surface area was significantly higher.

Finally, it should be mentioned that the dose to the subjects exceeded the value of 50 μm given in the protocol by 50 to 60 fold. The calculated total deposited mass in patient A21 is about 0.95 mg higher than that in the analyses provided by Dr. Kim (1.85 mg). Since this patient has a smaller than average lung size, it is likely that uncertainty regarding use of the default values contributed to the difference in deposition results. The calculated deposited mass in patient C05 matches that of Dr. Kim closely (2.5 mg versus 2.4 mg).

Table 1. Breathing parameters of the subjects during the exposures as provided by Dr. Kim.^a

Tidal Volume (cm ³)	Breathing Period (s)	Breathing Frequency (min ⁻¹)
350	4	15.00
350	2.8	21.43
500	6.66	9.01
500	4	15.00
500	2	30.00
750	6	10.00
750	4	15.00
750	3	20.00
1000	8	7.50
1000	4	15.00
1000	2	30.00

^a The functional residual capacity values supplied by Dr. Kim for subjects A21 and C05 were 3.05 and 6.91 liters, respectively.

Table 2. Deposited mass of particles in subject A21 with FRC =3.05 liters using a lung geometry with the smallest number of TB airways.

Number of Breaths	Deposition Fraction				Deposited Mass (mg)			
	Head	TB	PUL	Total	Head	TB	PUL	Total
8	0.275	0.163	0.366	0.804	0.039	0.023	0.051	0.113
11	0.346	0.169	0.311	0.826	0.067	0.033	0.060	0.159
8	0.189	0.181	0.481	0.851	0.038	0.036	0.096	0.170
11	0.271	0.178	0.42	0.869	0.075	0.049	0.116	0.239
10	0.354	0.333	0.23	0.917	0.089	0.083	0.058	0.229
8	0.209	0.184	0.511	0.904	0.063	0.055	0.153	0.271
11	0.263	0.24	0.416	0.919	0.108	0.099	0.172	0.379
10	0.287	0.335	0.312	0.935	0.108	0.126	0.117	0.351
6	0.176	0.186	0.559	0.922	0.053	0.056	0.168	0.277
7	0.249	0.329	0.366	0.945	0.087	0.115	0.128	0.331
7	0.208	0.7	0.075	0.983	0.073	0.245	0.026	0.344
Accumulated total mass (mg):					0.797	0.920	1.144	2.862

Table 5. Deposited mass of particles in subject C05 with FRC =6.91 liters using a lung geometry with the largest number of TB airways.

Number of Breaths	Deposition Fraction				Deposited Mass (mg)			
	Head	TB	PUL	Total	Head	TB	PUL	Total
9	0.479	0.149	0.002	0.63	0.075	0.023	0.000	0.099
9	0.568	0.122	0.002	0.693	0.089	0.019	0.000	0.109
6	0.366	0.277	0.032	0.675	0.055	0.042	0.005	0.101
11	0.496	0.208	0.03	0.734	0.136	0.057	0.008	0.202
10	0.653	0.153	0.021	0.827	0.163	0.038	0.005	0.207
8	0.384	0.282	0.133	0.799	0.115	0.085	0.040	0.240
11	0.478	0.227	0.128	0.833	0.197	0.094	0.053	0.344
9	0.542	0.201	0.116	0.859	0.183	0.068	0.039	0.290
6	0.312	0.317	0.211	0.841	0.094	0.095	0.063	0.252
7	0.453	0.223	0.209	0.884	0.159	0.078	0.073	0.309
6	0.573	0.208	0.147	0.929	0.172	0.062	0.044	0.279
Accumulated total mass (mg):					1.439	0.661	0.331	2.432

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Chong Kim

03/26/02 11:24 AM

To: Robert Devlin/RTP/USEPA/US@EPA

cc:

Subject: dose

According to the ICRP (International Commission on Radiological Protection) model, deposition dose of 1 and 3 micron particles is estimated at 4 and 42% of 5 micron particle dose, respectively. Because deposited particles are cleared out from the lung by 24 and 38% for 1 and 3 micron particles, respectively within 24 hours, the dose retained in the lung of 1 and 3 micron particles is expected to be 3 and 26% of the initial deposition dose of 5 micron particles, respectively. Therefore, the maximum dose for all three particles may be estimated to be approx. 1.3 times the dose of 5 micron particles.

Calculated values from one COPD subject was 0.14 and 0.83 mg for 1 and 3 micron particles, respectively, which was 3.5 and 5.8% of 5 micron dose (2.39 mg). Considering the clearance, the retained dose after 1 day would be 0.51 and 0.11 mg, respectively. Therefore, total dose for all three particles would be $2.39 + 0.51 + 0.11 = 3.01$ mg, which is 1.25 times the 5 micron dose. The experimental values are consistent with theoretical predictions. Although most of subjects came in for 5 micron particle study several days after 1 or 3 micron study (retained dose would be much lower), it may be reasonable to estimate the maximum dose by multiplying the 5-micron dose by 1.25 or 1.3.

Chong

Total Deposition of Therapeutic Particles During Spontaneous and Controlled Inhalations

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ABSTRACT: Treatment of systemic diseases by means of the inhalation route is hampered by uncertainties of the drug dose applied by inhalation. In this study, the hypothesis was tested that by standardization of the breathing maneuver used for inhalation, the interindividual variability of the dose deposited intrathoracically can be reduced. Therefore, breathing pattern during routine inhalations with jet nebulizers was measured in 18 patients with lung disease. Using monodisperse 3 μm particles, total deposition was then assessed for the measured spontaneous and for three controlled, slow breathing patterns. Particle deposition for the three controlled breathing patterns was additionally measured in 14 healthy subjects. The study has shown that within the study population the inhaled air volume and flow rate were quite different. Consequently, total particle deposition varied between 20 and 95%, depending on breathing pattern. For controlled, slow breathing patterns, deposition was on average higher, intersubject variability of deposition was smaller, and differences in deposition between healthy subjects and patients were negligible. Therefore, to perform efficient systemic treatment with aerosolized drugs, controlled, slow breathing patterns should be used. © 2000 Wiley-Liss, Inc. and the American Pharmaceutical Association *J Pharm Sci* 89: 724–731, 2000

Keywords: particle deposition; variability; breathing pattern

INTRODUCTION

For many decades it has been well known that drugs for systemic therapy may be administered by means of the lungs. Since 1925, it has been known that inhaled insulin decreases the blood glucose level.¹ Nowadays, despite considerable progress in nebulizer technique and increased knowledge about particle deposition in the lung and drug absorption from lung surfaces, insulin administration by means of the lung is still not established but has reached a state of advanced clinical studies. The main reason for this slow-

ness of progress is related to uncertainties in the dose of drug administered by the inhalation route. The dose depends on many factors that are difficult to control: particle deposition in the lungs strongly depends on particle size, lung structure, and breathing pattern, with the result that particle deposition and thus the deposited dose varies considerably among patients.

In this study the hypothesis was tested that standardizing the breathing pattern decreases the intersubject variability of the dose deposited intrathoracically during inhalations of therapeutic particles generated with jet nebulizers. Therefore, in 18 patients deposition of inhaled monodisperse inert test particles was measured for the breathing pattern they used during routine inhalations with jet nebulizers and for three standardized patterns. In addition, particle deposition was

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measured in 14 healthy subject for these standardized patterns.

METHODS

Subjects

Eighteen patients, 12 men and 6 women, who were used to aerosol therapy with jet nebulizers and 14 healthy subjects, 8 men and 6 women, participated in this study (Table 1). Eight patients had chronic obstructive pulmonary disease, seven patients had bronchial asthma, one patient had bronchiectasis, one patient had silicosis, and one patient had primary ciliary dyskinesia. Conventional pulmonary function tests were performed by use of a Jäger-Masterlab (Erich Jaeger GmbH, Würzburg, Germany). Relative values of the lung function parameters (%pred) were calculated as proposed by the European Community for Coal and Steel.² Informed written consent was obtained from each subject. The study protocol was approved by the Ethics Committee of the Medical School of the Ludwig-Maximilians-University (Munich, Germany).

Spontaneous Breathing Patterns

The breathing pattern of patients during routine inhalations with jet nebulizers (Pari-LC+ nebulizers, Pari GmbH, Starnberg, Germany, pressure 0.17 M Pa) was measured as follows: An ultrasonic transient-time flowmeter (TUBA, GHG AG, Zürich, Switzerland) was connected to the Venturi channel (air inlet) of the nebulizer. The analogous flow signal was recorded by a personal computer (Intel 386 CPU) with a analog-digital converter (Data Translation DT2821), and the flow rate through the nebulizer nozzle was added. This air flow through the nebulizer nozzle was

measured for each nebulizer before inhalation. All patients were instructed to perform inhalations as usual until 2.5 mL of a salbutamol inhalation solution (GlaxoWellcome, 1.5 mg salbutamol sulphate in isotonic NaCl solution) was completely nebulized. From the recorded flow rates of each breath the average spontaneous tidal volume, V_T , and flow rate, Q_T , were calculated for each patient.

Deposition

To measure total deposition of aerosol for various breathing patterns, a monodisperse inert test aerosol consisting of di-2-ethylhexyl sebacate (DEHS) droplets was used. Deposition measurements were performed using a device in which a laser aerosol photometer³ is combined with an piston-type ventilator, allowing the subject to inhale particles at controlled breathing patterns (Fig. 1). The ventilator has a volume of 2 L and is driven by a computer-controlled step motor. A system of computer-controlled magnetic valves allows us to connect the ventilator to ambient air, to an aerosol supply, or to a mouthpiece at which the subject wearing a noseclip is located. After the ventilator was filled with aerosol, the subject tried to inhale at the mouthpiece, causing an underpressure that initiated the step motor. Thus, aerosol is inhaled at a preselected flow rate, Q_T . After inhalation of the desired aerosol volume, the direction of the ventilator was inverted and the subject exhaled into the ventilator at the preselected flow rate.

During the entire breathing cycle the laser aerosol photometer recorded the respired particle number concentration. Aerosol particle deposition, D , was calculated by integrating the particle number concentration, C , over the inhaled, V_T ,

Table 1. Lung Function Parameters of the Study Population

Parameter	Patients		Normals	
Number	18		14	
Sex	12 m 6 f		8 m 6 f	
Age (yr)	60 ± 16		35 ± 6	
VC	31 ± 0.91	90 = 19% pred	5.5 ± 1.1	113 ± 10% pred
TLC	6.4 ± 1.11	103 = 14% pred	6.9 ± 1.1	107 ± 7% pred
ITGV	4.4 ± 1.51	143 = 42% pred	3.6 ± 0.71	112 ± 19% pred
FEV ₁	1.58 ± 1.11	66 = 34% pred	4.0 ± 0.91	106 ± 13% pred

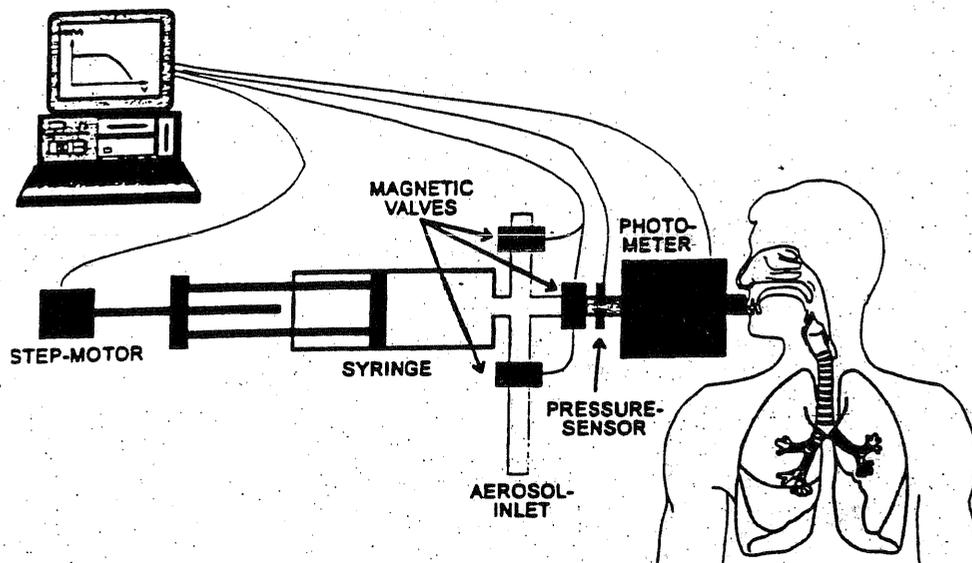


Figure 1. Schematics of the device for the measurement of lung deposition.

and exhaled volume, V_e :

$$D = 1 - \frac{\int_{V_i} CdV}{\int_{V_e} CdV}$$

In this study the following breathing patterns were performed by each subject:

Spontaneous breathing:

$$V_i = V_e = V_T, \quad Q_i = Q_e = Q_T$$

Very slow controlled breathing:

$$V_i = V_e = 1L, \quad Q = Q_e = 100 \text{ cm}^3 \text{ s}^{-1}$$

Slow controlled breathing:

$$V_i = V_e = 1L, \quad Q = Q_e = 250 \text{ cm}^3 \text{ s}^{-1}$$

Normal controlled breathing:

$$V_i = V_e = 1L, \quad Q = Q_e = 500 \text{ cm}^3 \text{ s}^{-1}$$

For each breathing pattern particle deposition was measured twice in each subject. Healthy subjects performed only the three standardized breathing patterns.

Particle Generation and Classification

Monodisperse di-2-ethylhexyl sebacate (DEHS) droplets were produced by heterogeneous nucleation of DEHS vapor on NaCl nuclei in a nitrogen atmosphere using a Topas SLG 270 generator

(Palas, Karlsruhe, FRG). The aerosol was then diluted with particle-free air to achieve a particle number concentration of $2 \cdot 10^4 \text{ cm}^{-3}$. Particle size was measured in a convection-free sedimentation cell and throughout the study was $2.98 \mu\text{m} \pm 0.1 \mu\text{m}$, a typical particle diameter for medical nebulizers.⁴

Data Evaluation

All statistical calculations were performed using Statgraphics Plus for Windows 2.0 on a personal computer (Pentium II CPU). The significance of differences between group averages was tested using the Student's *t* test. Correlation analysis was performed using Pearson product-moment correlation analysis. The requested level for significance was $P = 0.05$.

RESULTS

Although all patients were carefully trained at the beginning of their inhalation therapy to perform inhalations deeply and slowly, the breathing pattern was quite different among patients (Fig. 2). Some patients inhaled with a tidal volume of about 250 cm^3 and flow rates less than $200 \text{ cm}^3 \text{ s}^{-1}$, others inhaled about $2,000 \text{ cm}^3$ with flow rates close to $1,000 \text{ cm}^3 \text{ s}^{-1}$. The intraindividual variability of the tidal volume was $25 \pm 10\%$ and that of flow rate $22 \pm 10\%$. There was a strong correlation

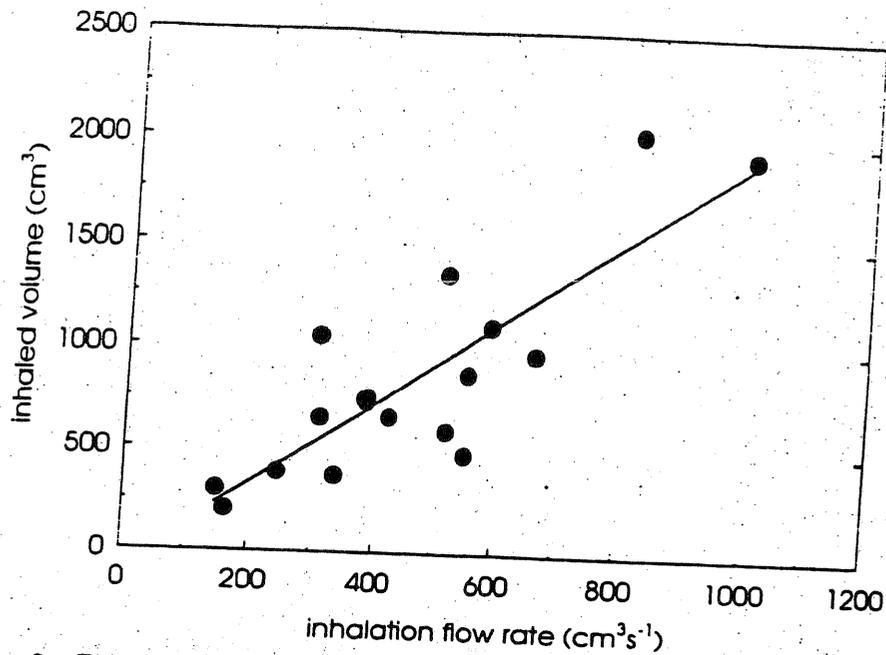


Figure 2. Tidal volume and flow rate measured in 18 patients with lung disease during spontaneous inhalations with a jet nebulizer.

between tidal volume and inhalation flow rate ($r = 0.84$, $P < 0.0001$): Thus, patients inhaling a large volume inhaled with a high flow rate; patients inhaling small volumes inhaled slowly with the result that the time of inhalation was nearly the same in all patients (1.8 ± 0.62 s).

Deposition of $3\text{-}\mu\text{m}$ particles for spontaneous breathing pattern correlated strongly with the flow rate ($r = 0.76$, $P = 0.0002$) (Fig. 3) and the tidal volume ($r = 0.75$, $P = 0.0003$): patients inhaling a large volume at a high flow rate showed high aerosol deposition and vice versa. Average

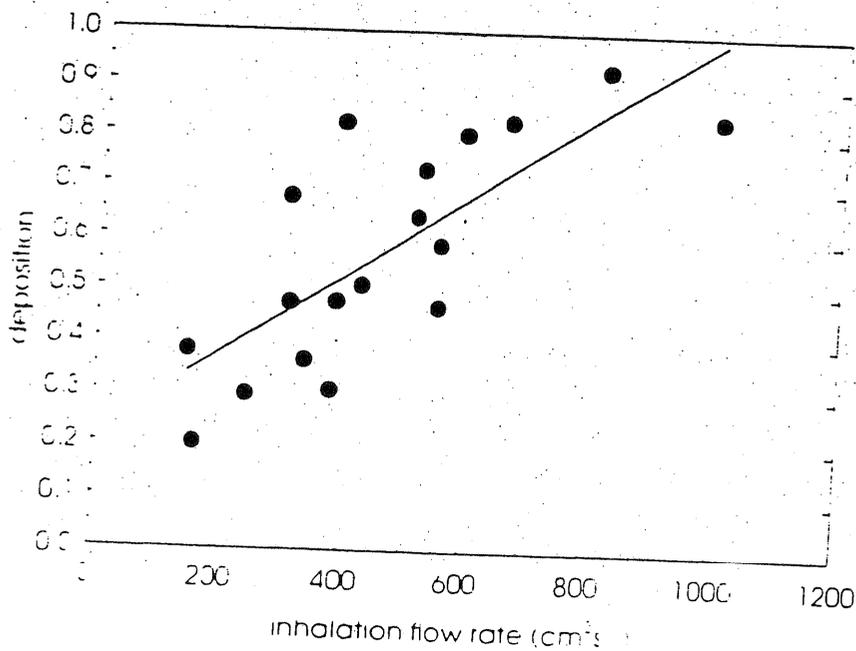


Figure 3. Particle deposition measured with test particles in 18 patients with lung disease as a function of inhalation flow rate.

total deposition in all patients was $(57 \pm 22\%)$, exhibiting large intersubject variability: one patient showed deposition as low as 20%, whereas another patient reached deposition values of 95%. This variability was considerably reduced for controlled breathing (Fig. 4). Deposition was highest and the variability was lowest for very slow controlled breathing ($79 \pm 7\%$). For the slow breathing pattern deposition was significantly lower than for the very slow pattern ($70 \pm 10\%$, t test: $P = 0.01$). The normal breathing pattern showed similar deposition values as the slow pattern ($71 \pm 13\%$, t test, not significant). There was a significant correlation between deposition and flow rate ($r = -0.20$, $P = 0.04$). For all controlled breathing patterns there were no significant differences in aerosol deposition between patients and healthy subjects (Fig. 5). However, deposition in patients tended to be greater for the largest flow rate, and the variability of deposition was larger in patients for all flow rates. In healthy subjects deposition decreased significantly with increasing flow rate ($r = 0.74$, $P < 0.0001$). Again, deposition for the very slow breathing pattern was highest ($79 \pm 7\%$), lower for the slow breathing pattern ($71 \pm 4\%$, $P < 0.0001$), and again lower for the normal breathing pattern ($65 \pm 7\%$, $P = 0.007$). At a flow rate of $500 \text{ cm}^3/\text{s}$, deposition in patients correlated negatively with the extent of airway obstruction as measured by FEV_1 ($r = 0.72$, $P =$

0.002) (Fig. 6). Except for this obstruction dependency of deposition, no dependency on the kind of lung disease was observed in patients. At lower flow rates and in healthy subjects no significant correlations were observed (Fig. 7).

DISCUSSION

In this study total particle deposition was measured, but it was not possible to distinguish between extrathoracic, bronchial, and alveolar deposition. However, the total deposition values measured in this study are similar to the values given by a common deposition model.⁵ For the very slow breathing pattern and for $3\text{-}\mu\text{m}$ particles this model delivers a total deposition of 80%, which is in excellent agreement with the data measured in this study, and an extrathoracic deposition of 1.6%. For the faster patterns total deposition is 69 and 58%, and the extrathoracic deposition increases to 4 and 7.5%. Bronchial deposition given by this model is 9% for the very slow pattern and 3.5 and 3.6% for the faster inhalations. Because extrathoracic deposition is supposed to be similar to that observed in healthy subjects in patients with lung disease, we conclude that total deposition measured in this study is a reasonable measure for intrathoracic deposition in humans.

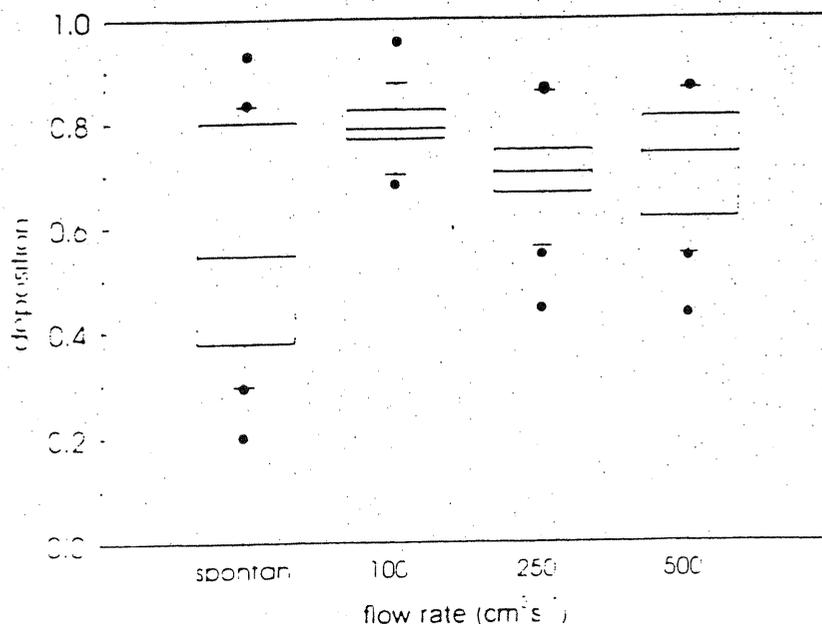


Figure 4. Particle deposition in 18 patients with lung disease at various breathing patterns.

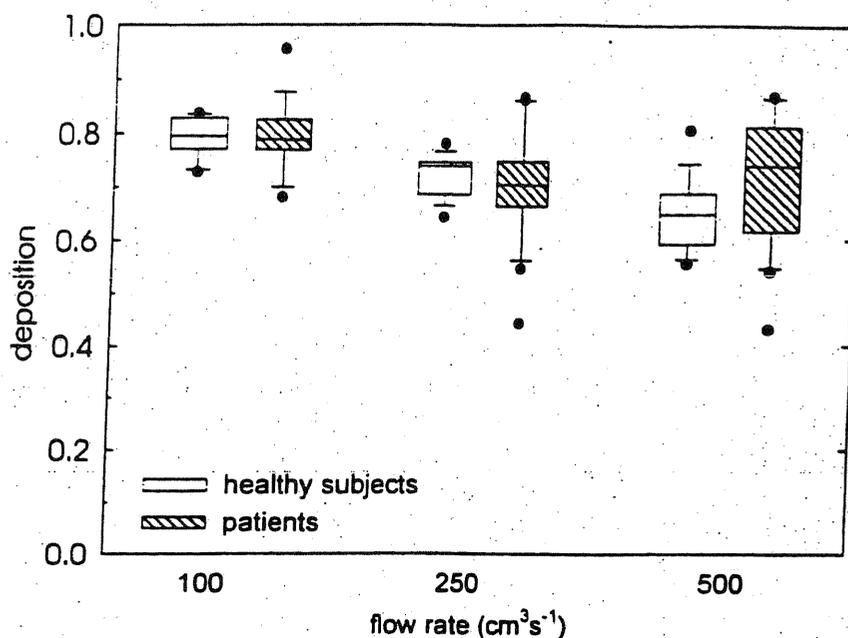


Figure 5. Particle deposition measured in 18 patients with lung disease and in 14 healthy subjects at three different breathing patterns.

For inhalation drug delivery requiring a precise dosage, the large intersubject variability of total deposition measured in this study for a spontaneous inhalation pattern is unacceptable. The data of this study show that the variability of particle deposition within the respiratory system can be considerably reduced if the breathing pattern

is controlled. The variability of deposition for the very slow breathing pattern was about three times smaller than the variability for the spontaneous pattern. This reduction in intersubject variability was air-flow rate dependent (Fig. 5). For slow and very slow flow rates deposition in healthy subjects and in patients is nearly identi-

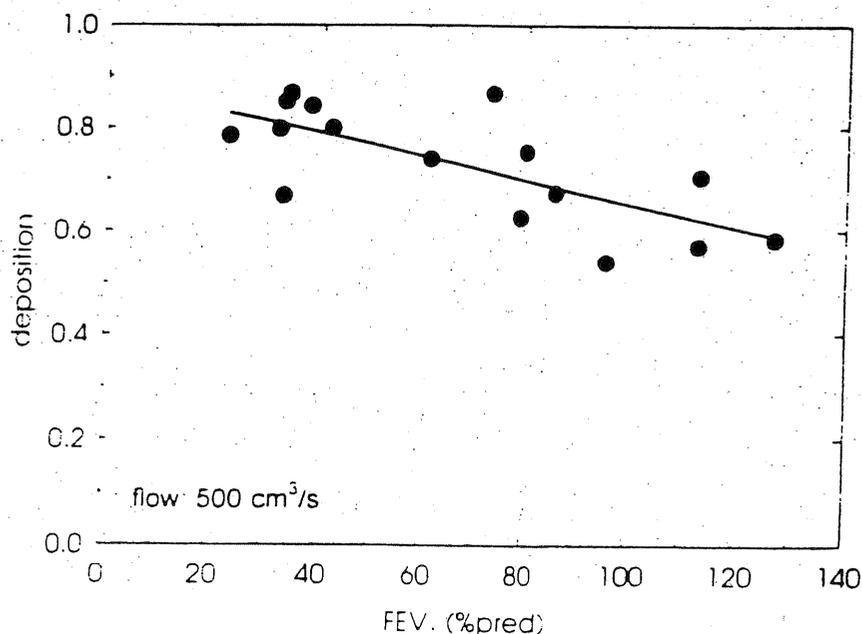


Figure 6. Particle deposition in 18 patients with lung disease at a inhalation flow rate of 500 cm³/s as a function of the forced expiratory volume in 1 s (FEV₁).

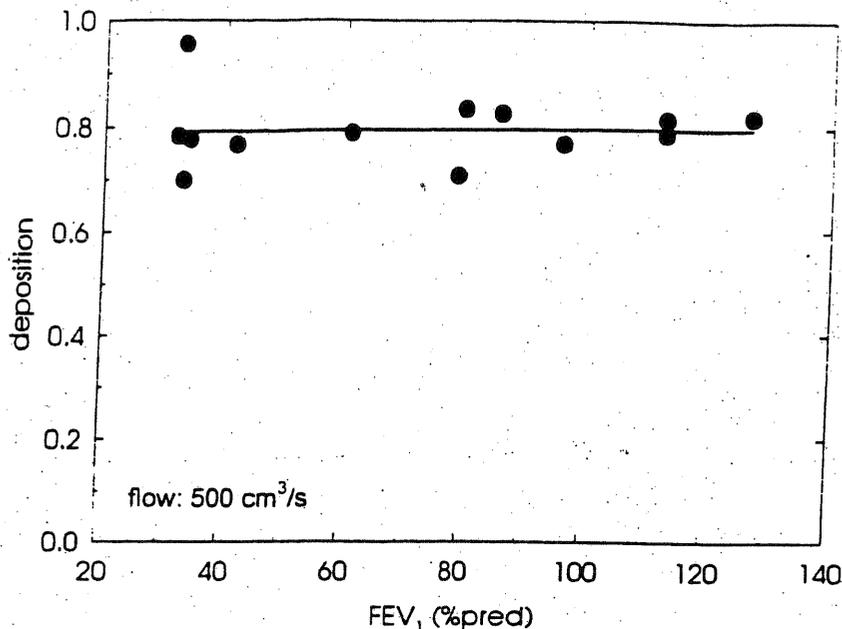


Figure 7. Particle deposition in 18 patients with lung disease at an inhalation flow rate of $100 \text{ cm}^3/\text{s}$ as a function of the forced expiratory volume in 1 s (FEV_1).

cal. Only for the highest air flow rate of $500 \text{ cm}^3/\text{s}$, patients tended to have higher deposition values than healthy subjects. If we assume that extrathoracic deposition is small, this difference may be explained by particle impaction in obstructed airways at higher flow rates.⁶⁻¹⁰ The strong correlation between FEV_1 and particle deposition (Fig. 6) illustrates that patients with normal FEV_1 (i.e., without airway obstruction) have the same deposition values as healthy subjects, whereas patients with decreased FEV_1 (i.e., with airway obstruction) show increased total deposition. This increase of total deposition in patients with airway obstruction is presumably due to increased inertial deposition within conducting airways. Because total deposition in patients and healthy subjects is the same for the very slow breathing pattern, it may be concluded that by inhaling very slowly, inertial deposition at obstructed airways can be prevented.

The implications of these results for an improvement of inhalation therapy are obvious. If a drug shall be applied to the lung periphery with high efficacy and low variability, inhalation should be performed slowly and controlled. In this case deposition is high (about 80%) and intersubject variability is low (9% for patients and 5% for subjects without lung disease), and deposition in obstructed airways may become negligible.

CONCLUSION

This study has shown that the intersubject variability of total particle deposition can be considerably reduced if the breathing pattern is controlled. If the inhalation flow rate is low, the variability is low and deposition at bronchial obstructions is supposed to be negligible. Therefore, the controlled breathing pattern with low flow rate is most suitable for targeting the lung periphery and thus for systemic aerosol therapy. If hormones like growth hormones or estradiol, heparin for surgery patients,^{11,12} α_1 -antitrypsin for patients with α_1 -antitrypsin deficiency,¹³ or prostacyclin for patients with pulmonary hypertension¹⁴ are administered by the inhalation route, this standardization of breathing patterns appears to be necessary.

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TECHNICAL SYSTEMS REVIEW CHECKLIST

Title: Determination of Deposition Dose of Inhaled Particles in Human Lung Airways
 IRP No. NHEERL-H/HSD/CRB/CSK/92-001-00
 ORD Subcomponent: H29001
 National Health and Environmental Effects Research Laboratory (NHEERL)
 U.S. Environmental Protection Agency
 Research Triangle Park, NC 27711

Review Date(s): August 25 & 27, 1997 Division: Human Studies Project QA Category: II
 Principal Investigator: Dr. Chong Kim, Ph.D. Location: EPA Building, Chapel Hill, NC
 Auditors and Affiliations: Dr. Jesse Mabellos (TSR Team Leader, NHEERL-RTP QA Manager), Mr. James Sutton (NHEERL-RTP QA Manager), and Dr. Vernon Benignus (Senior Scientist, HSD)
 Project Personnel Present: Chong Kim
 Completed by: Jesse Mabellos, Vernon Benignus, and James Sutton

REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
1. Is there a written and approved protocol for this study? If not, what document best represents the overall research goals, study objectives, and procedures for the conduct of the study?				Dr. Kim's Intramural Research Protocol (IRP) serves as the primary planning document for this study.
2. Are written and approved operating procedures (OPs) used in this study? If not, briefly describe how/where study procedures are documented.				An operating procedure (OP) "Bolus Aerosol Inhalation and Analysis" that pertains to bolus aerosol inhalation test in humans and subsequent analysis of data is developed for this study. Also, an OP "Operating procedure for MAGE generator to generate DES monodisperse aerosols" was created. In addition, an OP "Operating procedure of aerodynamic particle sizer and aerosol diluter" was generated for this study.

TECHNICAL SYSTEMS REVIEW
 Date: August 25 & 27, 1997

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 Principal Investigator: Dr. Chong Kim

REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
<p>3. Is the actual study design and conduct as specified in study planning documentation (e.g., OPs, protocols, work plans, QA plans)? If not:</p> <p>◆ Are changes/deviations clearly documented?</p>				
B. Quality Objectives and Performance Criteria				
1. Is the anticipated use of the data known and documented?				The purpose of the study is indicated in the IRP (Purpose section, pp 1-2). In the consent form to participate in a research study, the purpose of the research study is also provided to study subjects.
2. Have study quality objectives, consistent with anticipated data use, been established and documented?				
3. Have performance criteria for measurement data (e.g., detection limits, precision, bias) been established and documented?				Quality Control Requirements for this study are generally described on page 6 in the IRP. Section 5 (Evaluation Criteria) of the OP "Bolus Aerosol Inhalation and Analysis" specifies the desired inhalation flow rates and volume of the inhaled bolus. The default settings, which indicate the desired conditions to which the instrument must be set or adjusted for data collection, for various instruments are shown in Appendix A (Instrument Default Settings) of the OP.
4. Are there established procedures for assessing whether quality objectives and measurement data criteria have been met? If yes, briefly describe.				Quality Control Requirements for this study are generally described on page 6 in the IRP.

REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
5. Are there established procedures for corrective or response actions when measurement performance criteria or other quality objectives are not met? If yes, briefly describe.				For instance, in the "Consent to Participate in a Research Study" there are exclusion rules which specify when subjects are not allowed to participate before a test is administered or while a test process is on-going. In Quality Control section of the SOP "Bolus Aerosol Inhalation and Analysis," the data are discarded if the subject did not follow a breathing pattern procedure.
6. Are items 1-5 above consistent with study planning documentation (e.g., protocols, work plans, QA plans, OPs)? If not, are changes/deviations clearly documented?				
C. Study Organization and Personnel				
1. Are all the key study participants, roles, and responsibilities as specified in study planning documentation?				Study participants and their roles and responsibilities are indicated in the Personnel Assignments section of the IRP (p. 7).
2. How are new personnel trained? Where and how are these documents maintained?				Dr. Jeffrey Ding is on a post-doctoral training in this study.
3. How is communication linked among study participants?				
4. Are items 1-3 above consistent with study planning documentation (e.g., protocols, work plans, QA plans, OPs)? If not, are changes/deviations clearly documented?				
D. Facilities, Equipment, and Supplies				

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REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
1. List any key facilities (e.g., serum collection and analysis facilities), and briefly describe the major activities performed in support of the study. Indicate whether each facility is adequate. If not, briefly describe areas where improvements may be desirable or necessary.				The study is performed in a modern, state-of-the-art EPA Human Studies Facility in Chapel Hill, NC Equipment and Supplies are enumerated in the IRP (p 6) as well as in the OP "Bolus Aerosol Inhalation and Analysis."
2. List below key equipment used in the study. For each item, indicate whether testing, inspections, and maintenance are conducted regularly. If yes, specify:				Equipment and instruments are enumerated in the Equipment and Supplies section of the IRP (p 6). Quality control requirements, including instrument maintenance & calibration, are indicated in the Quality Control Requirement section of the IRP. Also, the default settings for various instruments which essentially are the conditions by which the instruments are maintained and calibrated for data collection are shown in Appendix A (Instrument Default Settings) of the OP "Bolus Aerosol Inhalation and Analysis."
◆ if acceptance testing, calibration, or inspection is done				
◆ frequency and range of calibration and calibration checks and the types of calibration standards used				
◆ person or organization responsible for performing calibration checks, inspections, and maintenance				
◆ if procedures are documented in an operating procedure				
◆ if a calibration or maintenance log is kept				
Condensation monodisperse aerosol generator				

REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
MAGE aerosol generator				Maintenance of the instrument is covered in the OP "Operating procedure for MAGE generator to generate DES monodisperse aerosols." Calibration of the flow rate of the MAGE system is indicated in the OP "Bolus Aerosol Inhalation and Analysis."
Aerodynamic particle sizer (APS)				The measurement accuracy of this instrument will be examined weekly by sampling latex particles with certified diameter. Maintenance and set-up of the default settings of the instrument is covered in the OP "Operating procedure of aerodynamic particle sizer and aerosol diluter."
Scanning mobility particle sizer (SMPS)				The measurement accuracy of this instrument will be examined weekly by sampling latex particles with certified diameter.
Aerosol diluter				Maintenance and set-up of the default settings of the instrument is covered in the OP "Operating procedure of aerodynamic particle sizer and aerosol diluter."
Laser aerosol inhalation system				
Condensation particle counter				
Ultrafine condensation particle counter				
Gilibrator flow calibrator				
Flow-volume monitor and computer interface				
Letec medical nebulizer				
Rotameters				
3. Is acceptance inspection or testing performed on any supplies and consumables used in this study? If yes, list each supply/consumable below and briefly describe inspection or testing procedures and associated acceptance criteria.				
4. Are acceptance testing, inspection, maintenance, and calibration procedures performed as specified in study planning documentation (e.g., OPs, protocols, work plans, QA plans? If not, are changes/deviations clearly documented?				

REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
E. Pulmonary Function Test				
1. Are there written and approved procedures for the study personnel to follow when collecting, identifying, and storing the raw data? If yes, list below and note whether they have been distributed to all appropriate study personnel collaborating in the study. If not, briefly describe how/where these procedures are documented.				The methods (e.g. subject groups, pulmonary function test, etc.) and records and record keeping are tersely described on pages 2-6 of the IRP. Additional procedures are indicated in the OP "Bolus Aerosol Inhalation and Analysis."
2. Briefly describe any checks that are made to verify that study personnel are complying with the procedures described in Item 1 above.				
3. Can each raw data from pulmonary function test be traced to a specific study subject identifier, medical history, personality profile, blood screening test, questionnaire, and raw data collection date?				
4. Do the blood samples and urine samples require special treatment conditions? If yes, briefly describe the conditions and any documentation that these conditions were maintained from data collection through data analysis and archiving.				
F. Sample Analysis				
1. Are calibration records of each and all equipment and instrument clearly linked to raw data analysis?				

REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
2. Is the calibration range for each and all instrument and equipments appropriate for the raw data analysis performed?				Effects of particle size (ultraline, fine, and coarse particles) on lung deposition will be investigated in all study subjects. For APS two different size latex particles will be used (1.01 and 2.06 um diameter), whereas latex particles with 0.06 and 0.10 um diameter will be used for calibrating SMPS. Measured particle size will be maintained within plus or minus 5% of the size of the certified latex particles.
3. Are controls run? If yes, briefly describe.				
4. Are other routine QC checks performed on each and all instrument and equipment? If yes, briefly describe.				
5. Are the treatment and use of QC data clearly documented? If yes, briefly describe.				
6. Are data transformations/calculations and units clearly documented?				
7. How are data collected and analyzed?				
8. Are the dates of data analyses documented?				Data collection and analysis are presented in the Data Collection and Analysis section of the IRP (p. 5) using ASYST software (by Keithly Instruments Inc.).
9. Are the persons who performed the data analyses clearly identified?				
10. Are items 1-9 above performed as specified in study planning documentation (e.g., OPs, protocols, work plans, QA plans)? If not, are changes/deviations clearly documented?				

REVIEW QUESTIONS	RESPONSE				COMMENTS
	Y	N	NA		
G. Quality Assessments					
<p>1. Have any of the following external or self-assessments been conducted or planned for this study or for components of this study (e.g., support facilities, data management procedures)? If yes, briefly describe.</p> <ul style="list-style-type: none"> ◆ peer review ◆ performance evaluation ◆ data quality assessment ◆ Institutional Review Board 					The project has been approved by the Committee on the Protection of the Rights of the Human Subjects at the University of Carolina at Chapel Hill.
<p>2. Are these assessments conducted or planned as specified in study planning documentation (e.g., QA plans)? If not, are changes/deviations clearly documented?</p>					
H. Recordkeeping and Data Management					
<p>1. Is there an index list and description of all data, records, and specimens to be maintained for this study?</p>					
<p>2. Are all study records (e.g., floppy disks, log books, notebooks, instrument outputs, samples/specimens, correspondence) clearly cross-referenced (e.g., by protocol number, date, experiment number)? If yes, briefly describe.</p>					All pulmonary data are stored on-line in a centralized computer system which is managed by TRC Inc. under contract to EPA (Records section of the IRP, p. 6). Additional record keeping procedures are indicated in the Record Keeping section of the OP "Bolus Aerosol Inhalation and Analysis."

REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
3. Is there an individual responsible for logging and compiling all study data and reporting to the lead principal investigator?				Study participants and their roles and responsibilities are indicated in the Personnel Assignments section of the IRP (p. 7).
4. How are study data, records, and specimen stored?				All pulmonary data are stored on-line in a centralized computer system which is managed by TRC Inc. under contract to EPA (Records section of the IRP, p. 6). The raw data are stored by ASYST data format as indicated in Appendix B and Appendix B1 of the OP "Bolus Aerosol Inhalation and Analysis."
5. Are hand-written records recorded in numbered or otherwise uniquely identified notebooks or binders which are assigned to individual staff members?				
6. Are all data files and samples named according to a standard convention? If yes, briefly describe.				The raw data file naming strategy follows the ASYST data format as indicated in Appendix B and Appendix B1 of the OP "Bolus Aerosol Inhalation and Analysis."
7. Are there procedures for routine verification of the raw data collection and management activities listed below? If yes, briefly describe and note whether verifications are documented in study records. <input type="checkbox"/> Hand recorded data <input type="checkbox"/> Data entry (e.g., keyboard) <input type="checkbox"/> Computerized data transfers <input type="checkbox"/> Computer-generated data <input type="checkbox"/> Computer-transformed data and graphs				

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Principal Investigator: Dr. Chong Kim

REVIEW QUESTIONS	RESPONSE			COMMENTS
	Y	N	NA	
8. How are data reduction, transformation, and analysis procedures documented?				Statistical analyses of the data are performed as specified in the Data Collection and Analysis section of the IRP.
9. Are all data records identified with a test/sample ID number and a protocol or study number?				
10. Are items 1-9 above as specified in study planning documentation (e.g., protocols, work plans, QA plans)? If not, are changes or deviations clearly documented?				

EXIT BRIEFING SUMMARY

A. EXEMPLARY FINDINGS

1. The purposes of the review were satisfactory to the reviewees. These purposes were:
 - * research planning is appropriate to assure that the quality of the research and resulting data are adequately addressed,
 - * research is being performed as planned as well as whether documentation exists to confirm that such is the case, and
 - * the quality or uncertainty of the data is reported to those who may use it.
2. Peer review. A previous peer of the research had been conducted and the potential for bias in the results because of asymmetry in pulmonary functions was adduced as a potential problem in the research model. It was felt that Dr. Kim's sample size is probably sufficient to swamp any bias that results from this variable.
3. Facilities. Dr. Kim's laboratory is housed in an excellent facility, well-equipped, and adequate for the purpose. All areas are clean, free of clutter and well maintained.
4. Aerosol Inhalation System. Dr. Kim has designed the aerosol inhalation system that is adequate for the purpose of the collection of this data. All components of the system are well-maintained and calibrated.
5. Documentation. Dr. Kim's laboratory has written an Intramural Research Protocol (IRP) that is closely followed. The IRP describes the project-specific QA/QC efforts: thorough, easy to follow Standard Operating Procedures (SOPs); study records are kept in a centralized computer system and/or on computers disks with backup tapes which are kept in the PI's and co-PI's offices. In addition, a published research article is available which describes experimental procedures and other processes.
6. Archives. All pulmonary function data are stored on-line in a centralized computer system which is managed by TRC, Inc. Each subject's records and subject selection data are kept in a centralized computer system managed by Bionetics Inc. These records are secure and available to the researchers.
7. Communication. Study investigators are located on the same floor of the building and offices are very accessible. They meet regularly to discuss study progress and resolve problems. Additionally, Dr. Kim is actively involved in the study and reviews and signs each subject's Informed Consent Forms and answers subject's questions.

B. RECOMMENDATIONS FOR IMPROVEMENT

1. Finding: Electronic and manual data forms for data collection or for instrument maintenance and calibration did not include the name or signature of the person gathering data or maintaining/calibrating the instrument when such activity was performed.

Discussion: The name of the person and/or signature in the data forms is important in order to provide accountability to the person doing that specific work. Personal accountability becomes even more important as additional people become involved in the operation, maintenance, or calibration of the inhalation system as well as for data acquisition, data reduction or data analysis. The specific work done by each personnel can be tracked. In addition, the date in the forms is important to provide traceability when a piece of work is done and who did it and to provide a mechanism for cross-referencing study records. Naming, initialing, and dating each provides a mechanism for verifying data documentation.

Because the overall quality and defensibility of the study can only be assessed through evaluation of the study records, it is important that uniform recordkeeping practices be consistently employed by all individuals responsible for operation, calibration, data acquisition, analysis, and reporting.

2. Finding: Access to computer files that control the aerosol inhalation system and maintain subject data were not password protected. The possibility of compromising the integrity of the data exists.

Discussion: A password provides a mechanism of control of access to the computer, instrument, program, and the data stored in the disk of the computer. Password-protecting computer and instrumentation files allow access only by qualified and authorized people, thus preventing accidental changes to the data or the data from being made available to unauthorized individuals.

3. Finding: Chemical analysis of the sebacic acid was not performed to check for purity or possible contamination. In addition, the lot number of the chemical was not documented.

Discussion: Because human subjects are involved in the study, protection of subjects and reducing risks must be important issues. The risk to the subjects can be prevented or greatly reduced by having a chemical analysis done on the chemical by a credible testing facility to provide certification of chemical purity and freedom from contamination by substances which may be harmful to the subject, the data gathering apparatus, or interfere with analysis. By recording the lot number, it can be traced easily through the manufacturer. Recording the lot number has an additional advantage in that if any suspected variability in responses by subjects to the chemical that could be attributed due to lot by lot variability, the problem can be tackled easily by reanalyzing the different lots.

It is also recommended that the package insert or label containing the manufacturer's

analysis be placed in the research documentation. This analysis should be reviewed for acceptability by the investigators and that acceptability documented. The team may also consider establishing specific rejection criteria.

4. Finding: It was not clear from the documents available what software or whether ASYST itself was used to perform for data reduction and/or for statistical analysis. Only during interview that it became clear that ASYST program was used from beginning to end of the data manipulation process: from raw data capture to data reduction to statistical analysis. Since there has been several versions of ASYST and the program updated constantly by installing update versions, the versions number of ASYST used were not documented.

Discussion: Because access to and retrieval of the computerized data can only be made with the correct version of the software, the version number must be documented and stored with the appropriately collected data. When the software is upgraded, the old version must also be archived with the appropriate data. It was recommended that the study records document which set of data were either collected or reduced with which version of the software. It was also recommended that previously reduced data be re-reduced using the newer versions for parameters of interest and comparisons made with results from the previous version to assure that consistent formulas between versions are used and that they have been debugged.

5. Finding: Two different sets of raw data records - one for the PI and another by the co-PI - are kept in the offices.

Discussion: This will have a consequence that, in case, one of the PIs is not available, the other person cannot easily and efficiently reconstruct the data. It is recommended that each of the PIs keep identical copy of the raw data. Since the project have duration of some several years before the data from this project may be exhaustively communicated to the scientific community, electronic degeneration of the diskettes may occur which poses a great risk of losing data if there is only one copy of floppy diskette kept by the PI.

6. Finding: Because the electronics may wander over time, a record of calibration to detect trends over time was not available (e.g., a 3 μ m reading several years ago may become 3.2 μ m this year and may further change over time).

Discussion: A QC chart of baseline data is recommended to detect long range electronic drift. A QC chart provides a graphical representation of trends over time. If the trend line surpasses limit lines (above or below), this provides a mechanism to either recalibrate or replace to a new electronic mother board. If a new electronic board is replaced, it has to be calibrated accurately and performs similarly as the previous board at its optimal level.

NOTE: As a preliminary on training and documentation of the qualifications of personnel, when Dr. Ding becomes an integral part of the research involved in data collection or operations of the inhalation system, a record of his qualification and training should be available. Any research

article may be provided which depicts his skills/expertise with the use of similar techniques, procedure, or processes in the project. If appropriate, new staff should have some record made of their skills specific to the apparatus which they will use.

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF JAMES BROWN

On May 11, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. JAMES BROWN, Health Scientist, National Center for Environmental Assessment, Office of Research and Development (ORD) at his office, Building B, Room # B220I, at the EPA Facility at Research Triangle Park (RTP), NC. BROWN was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

BROWN stated he began his employment at EPA in December 2003 and was a post-doctoral fellow at the University of North Carolina (UNC) when he was assigned about February 2001 to replace SHU-CHEIH HU to be a co-Principal Investigator to Dr. CHONG KIM's study of particulate matter deposits of di-2 ethylhexyl sebacate (sebacate). HU was moving to Chicago, IL and was teaching BROWN how the system used for KIM's sebacate study worked.

BROWN referred to his notes and his written summary of events from August 14 - August 17, 2001 (Attachment 1). BROWN stated the summary was from his original electronic file created at the time of the event and the hand-written changes were the result of his editing for readability this date prior to meeting with the reporting agent. BROWN showed the reporting agent the electronic file, titled 'subjconc.wp', which was last modified August 20, 2001 at 5:21 am.

BROWN stated before he was a graduate student, he was an Occupational Safety employee with Honeywell, and because of his experience with occupational safety, liked to know what people were exposed to when he was involved (in this case, as a co-principal investigator to KIM). BROWN stated JACKY ROSATI (also now BROWN's spouse) was a graduate student at the time working with KIM on another study, and when they compared studies, BROWN became aware that there may have been a problem in the amount of sebacate inhaled by subjects of KIM's study. BROWN stated it became obvious to him because in his experiments for KIM, he

Investigation Conducted on: May 11, 2005	Conducted at: Research Triangle Park, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 12, 2005	Prepared by: SA David L. Cotner <i>DL</i>

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EPA Form 2720-15 (Computer)

could visually see particle matter. With ROSATI's experiments, he could not see particle matter. BROWN stated ROSATI's lab set-up was used to conduct test's of the study BROWN was working.

BROWN stated after running the tests, and referring to the written summary, he made preliminary calculations which demonstrated the subjects were exposed to sebacate at 20 - 30 times the amount they consented to receive. BROWN notified KIM immediately and stated he became concerned when KIM did not address the problem the way BROWN believed it should have been addressed. BROWN stated he would have expected KIM to lower the concentration of the sebacate to what the protocol was or to revise the protocol. BROWN stated when he did not see KIM making those adjustments, he reported the incident to Dr. BROMBERG within a couple days.

BROWN did not believe there was any intent by KIM that caused the over-exposure of sebacate. BROWN stated his involvement ended that Friday, the day after the incident was reported to BROMBERG. BROWN stated he later (a few weeks) did some calculations for KIM to give the information to Dr. LINDA BIRNBAUM. BROWN stated he was never interviewed by the external review panel regarding his findings. BROWN stated no other substances were used other than sebacate during KIM's study.

BROWN did not believe there was any evidence to question the calculations of exposure until he did after comparing the study with the study ROSATI was working on. BROWN believed KIM should have known there was a risk of over-exposure because of the increased size, but did not believe anyone knew, including HU, of the over-exposure. BROWN stated he could not quantify his suspicion until it became clear from seeing ROSATI's study on August 14, 2001, and after BROWN reviewed the protocol and made calculations.

Regarding any allegation of cover-up, BROWN opined that a 'high degree of attention (was) given to it' by EPA management. BROWN cited a second example of a study that shut down the Human Subjects facility for testing. BROWN also cited the external review, including Dr. FRED MILLER's public review.

When asked why he thought these allegations were brought forward, BROWN opined Dr. TED MARTONEN may have made the allegation. BROWN stated it was known MARTONEN had differences with BIRNBAUM, including assignment to a different building and different workspace.

Attachment

1. Written summary of events August 14 - 17, 2001

uesday, 14 ~~September~~ ^{August} 2001

Generated a 5 um DESH aerosol and made measurements of aerosol concentration using Data Ram. The concentration as measured by the photometer at the mouthpiece fluctuated between 4-4.25 volts. For this condition, the Data Ram showed 10 mg/m³, although it only has a 34% efficiency for a 5 um aerosol, suggesting a real concentration of 29 mg/m³. Jacky and Chong were both present while these measurements were made as they were trying to look at the stability of her system versus the system which I am now using for Chong. That the aerosol concentration was very high was mentioned by me to Chong. It is worth noting that typical photometer readings recommended by Shu Chieh were 9 volts for bolus deliveries and 7.5-8.5 volts (never less than 6 volts) for tidal aerosol breathing, double the voltage when Data Ram measurements were made. Hence, aerosol concentrations used in experiments would be in the range of 59 mg/m³ for the 5 um aerosol.

Before a brief meeting with Bill and Dr. Bromberg, I mentioned the high concentrations to Bill. I said that the Data Ram read 10 mg/m³, but that I thought they might be as high as 50 mg/m³ during studies. He noted that he thought that they might be high when he had inhaled on the system.

The fact that the experimental aerosol concentrations were in excess of those presented in the study's Informed Consent Form were presented to Chong later in the afternoon. I said that before more subjects were studied that we needed to either revise the protocol or reduce the aerosol concentration. I said that a few weeks should be devoted to measuring the concentration at each particle size across a range of photometer voltages, which would also accomplish a linearity check of the system. Chong stated that, "at a lower voltage the signal to noise ratio would be too high." I replied that the consent form must be then be changed because people were being told that they were inhaling 50 ug. Chong came into my office at that point and we discussed a hypothetical case, if 100 liters were inhaled at 10 mg/m³, then a subject would actually inhale 1 mg or 1000 ug. I again pointed out that this was a large discrepancy and that in light of the recent Hopkins' incident we needed to change the study or the protocol. Chong stated that, "perhaps the protocol could be revised next year." The current Consent Form expires June 2002.

Soon after talking to Chong, Bill walked down the hall. I told him Chong's response. Bill stated that he did not think that the concentration was unsafe. I stated that, "Its not up to us to decide what is safe. That is a discussion for the Human Subject committee and that at any rate it is wrong to tell the subjects that they will inhale 50 ug when they actually inhale 1-1.5 mg." Bill stated that he did not think it was dangerous. Soon afterwards, Bill laughingly stated that his protocol said that people would inhale up to a 1 mg and that the photometer voltages used on upstairs were around a volt.

Frustrated and concerned, I talked about this problem with Bill McDonnell. His thoughts were that it was a breach of contract with the subjects and the Human Subjects Committee to knowingly have people breath more aerosol than the had agreed to. He also agreed that it was not for us to decide if the inhaled concentration was safe and that it was wrong to do so.

Wednesday, 15 ~~September~~ ^{August} 2001

Following a group meeting and a meeting with Mike Madden, there was a short meeting between Chong, Bill, Dr. Bromberg, and me to discuss bringing in a new post-doc for Chong. This post-doc was to work, partially with Chong on the ADEPO study, and with Bill and me

and said, "just wanted to let you know that you did the right thing, Elston had^s called the Human Subjects Committee, the protocol is suspended, and Chong is to write a letter stating how the error occurred."

Friday morning, 17-^{August}~~September~~ 2001

I saw Bill in the hall and told him with that I had heard that Chong's protocol was temporarily canceled and the Chong had to write a letter to the Human Subjects Committee telling them how the error had occurred. Bill stated the he already knew and that he had talked to Chong on Thursday evening. He said that Chong stated that he, "was already planning to do something about the protocol," implying that he was planning to do something before being confronted by Samet. Bill noted, "Although that is easy for him to say now, whether he was or not." Bill also stated that he was going to sit down with Chong and me and talk about this sometime soon. Bill then stated, "Chong said he was unhappy with the way the whole situation was handled. I {Bill} told him that I was too." I said to Bill, "I could not in good conscience sit with subjects as part of that study." Bill stated, "well you wouldn't have to."

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF LINDA BIRNBAUM

On May 4, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. LINDA S. BIRNBAUM, Division Director, Experimental Toxicology Division, Office of Research and Development (ORD), National Health and Environmental Effects Research Laboratory (NHEERL) at her office, Building B, Room # B141D, at the EPA Facility at Research Triangle Park (RTP), NC. BIRNBAUM was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

BIRNBAUM stated she was the Acting Director of Human Studies Division (HSD) from about February 2001 through February 2002. BIRNBAUM recalled Dr. JAMES SAMET, Principal Investigator, HSD at the University of North Carolina (UNC), first informed her of the over-exposure given to human test subjects of a study CHONG KIM was conducting. BIRNBAUM stated when told by SAMET of the dosage error, she immediately halted the study. A cursory evaluation was completed, which included the Institutional Review Board (IRB) located at UNC, over the course of several weeks. She stated the final result of the review was KIM was banned permanently from conducting any more human studies.

BIRNBAUM referred to her notes to ensure a more accurate recollection of events of the time frame and stated on August 16, 2001, she was told by SAMET of the incident. She stated she told SAMET to stop work on the study, to tell Dr. ELLSTON SEAL, then the EPA Human Ethics official, and to call the IRB to begin determining what happened. She stated Dr. ZENICK, her supervisor, was notified within a day. BIRNBAUM stated Dr. FRED MILLER, an expert at reviewing studies similar to KIM's, was brought in to review the calculations. MILLER made recommendations after his review.

BIRNBAUM stated those involved in the review at the time, did not think the mis-calculations of the excessive dosage was a serious health problem. No one thought the dosage level actually given 'imperiled the health of the patients'. BIRNBAUM opined the problem may have occurred due to the sloppiness of KIM because he did not account for mass of the particles as they

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increased in size. BIRNBAUM stated she was not part of the peer review of the KIM incident.

BIRNBAUM stated JIM BROWN, a Post Doctorate student at UNC at the time, assisted KIM on the study and was the person who first brought the information forward that there was an error calculating the mass as the size level of the particulate matter increased. BIRNBAUM stated BROWN told KIM of the error and KIM stopped his study at the time to review the measurements. BIRNBAUM believed KIM may not have looked at the problem as a serious issue because he did not see the excessive dosage as a health problem. BIRNBAUM's recollection was BROWN told his boss, Dr. PHIL BROMBERG, of the incident within a day because BROWN was not comfortable with how he perceived KIM handled the issue. BROMBERG stated the information needed to be reported to the IRB. BIRNBAUM recalled BROWN was upset over KIM's handling of the situation, so BROMBERG could not ignore what BROWN told him. BIRNBAUM stated Dr. STEVE BERNARD was the chairman of the IRB. Dr. DAN NELSON was also a member of the IRB. BIRNBAUM stated the IRB consisted of UNC personnel and one 'community person' (not a UNC or an EPA member).

BIRNBAUM stated she believed KIM was 'arrogant' the way he conducted his study, which led to his mistakes and sloppiness. She did not believe KIM had any intent to make mis-calculations that affected the study. BIRNBAUM believed KIM did not see the connection of by-passing the IRB for notification if there were no health effects to the subjects of the excessive dosage. She stated the IRB did approve changes to KIM's study, but neither the IRB, nor KIM, identified increased particle size would affect mass. BIRNBAUM stated she believed if the checks were sent through a supervisor and a human ethics official, the missed calculations affecting mass may have been identified. At that time, the review of a supervisor and a human ethics official was not required. It is now required as part of new policy.

While referring to her notes, BIRNBAUM stated on August 20, 2001, MIKE RAY, an EPA Quality Assurance official, stated KIM's work may have been shoddy research, but there was no evidence of intentional fraud.

BIRNBAUM stated she was currently Dr. TED MARTONEN's supervisor, and had been so for about 13 of the past 15 years. She stated MARTONEN had co-authored a mathematical modeling paper with KIM a few years ago. She stated although KIM can no longer conduct studies on humans, he can take part in research. BIRNBAUM recalled the article was also authored by a UNC Post Doctorate student, whom she could not identify. BIRNBAUM had not seen any differences of opinion between MARTONEN and KIM related to the article.

Related to the first allegation, BIRNBAUM recalled the test subjects were exposed to about 20, maybe 30 - 50 times the amount of the di-2-ethylhexyl sebacate as they had consented to. She stated the allegation of receiving a level of 100 times what the subjects consented to seemed high. BIRNBAUM stated if MARTONEN believed the exposure was 100 times what the subjects consented to, MARTONEN 'exaggerates'. In answering the second allegation of a cover-up, BIRNBAUM stated there was not a cover-up and NHEERL management had gone public with the information within a day of learning of the problem. BIRNBAUM stated numerous people were involved in discussions of the matter, involving both EPA and UNC personnel.

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INTERVIEW OF TED MARTONEN

On May 11, 2005, SA DAVID L. COTNER, Special Investigations Unit, and SA JERRY POLK, OI, Research Triangle Park (RTP), interviewed Dr. TED MARTONEN (919/541-7875), National Health Environmental Effects Research Laboratory (NHEERL), in his office, RTF Building, room number 2134 at Research Triangle Park, NC. MARTONEN was shown proper identification by reporting agent and POLK. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC) by MARTONEN, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

MARTONEN gave reporting agent his Curriculum Vitae (Attachment 1). MARTONEN stated he and his attorney, JOHN LOFTIN, spoke to MATTHEW GLOVER of OSC twice by conference call concerning MARTONEN's allegations of exposing subjects to a potentially dangerous substance and an EPA cover-up. The first conversation occurred during December 2004. The second, during January 2005. MARTONEN opined he had been harassed by EPA management. MARTONEN stated Dr. LINDA BIRNBAUM was his supervisor.

MARTONEN stated he called GLOVER because of his on-going Equal Employment Opportunity Council (EEOC) lawsuit against EPA. MARTONEN stated he was represented in that matter by LOFTIN. MARTONEN stated the EEOC hearing was scheduled for June 7 - 9, 2005 at the Federal Center. MARTONEN stated the basis for his claim was discrimination based on age, handicap, and reprisal because EPA would not accommodate his handicap. MARTONEN stated his motivation to call GLOVER resulted from his belief humans were used as 'guinea pigs' in Dr. CHONG KIM's di-2-ethylhexyl sebacate (sebacate) study when they were exposed to sebacate in excess of what they consented to receive. MARTONEN wanted to make that part of his EEOC case, but Judge REGINA N. STEVENS (federal judge) ruled it was inadmissible because MARTONEN lacked standing because he was not the subject of KIM's study. MARTONEN believed it was 'Nazi-like' to use humans as 'guinea pigs'.

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MARTONEN stated KIM's experiment that resulted in over-exposure happened about five years ago. MARTONEN stated he first reported it to the EPA administrator about 2002. MARTONEN stated his EEOC case became official in 2002 as well.

MARTONEN stated he wrote letters on EPA letterhead to EPA Administrator STEVEN JOHNSON twice; about seven or eight letters to Governor MICHAEL LEAVITT; and about five to ten letters to Governor CHRISTINE TODD WHITMAN. MARTONEN stated all the letters to the Administrators were sent by Express Mail and LOFTIN had copies of all the letters.

MARTONEN stated he authored two publications with KIM. One was a Human Health Studies of Healthy Subjects written in 1996 or 1997. The other article was about sick subjects written in 1997 or 1998. MARTONEN stated the raw data of the over-exposure of sebacate from KIM's study was in the log book kept by EPA. MARTONEN stated he saw KIM's log books in about 1997 or 1998. MARTONEN stated he told BIRNBAUM of the over-exposure after he reviewed the log books. MARTONEN stated he did not have any documentation (e-mail, memorandum, etc.) he had written to BIRNBAUM making the accusation of the over-exposure. When told by the reporting agent documentation would help substantiate his claim, MARTONEN stated he would check his files for any documents. MARTONEN stated he was qualified to review the log books and that there are only 800 to 1000 people qualified in the US, at places such as Harvard, Cal. Tech, University of Michigan, or other places with doctors of Pulmonary medicine.

MARTONEN opined Dr. FRED MILLER, who conducted a review and performed calculations of KIM's studies, and determined there was an over-exposure of sebacate to what the subjects consented to receive of 50 - 60 times, was both "qualified and not qualified" to make that determination. MARTONEN thought MILLER was qualified with his training and expertise, but not qualified because he was a long ago former employee of EPA who held BIRNBAUM's position when he was employed with EPA. (AGENT's NOTE: MILLER left EPA in the late 1980's).

MARTONEN stated part of the evidence of the violation was the fact that former Assistant Administrator Dr. PAUL GILMAN responded to one of MARTONEN's letters and admitted the human subject experiments occurred. MARTONEN again stated the subjects were exposed at a rate of 100 times what they consented to receive, but could not offer any documentation to support that claim. MARTONEN based that claim on his review of KIM's data contained in the log books related to KIM's study. MARTONEN stated he told BIRNBAUM of the over-exposure of sebacate by KIM about 1997 as a result of a professional article he was researching which would simulate experiments and make a math model. MARTONEN alleged BIRNBAUM started harassing him as a result of that claim. MARTONEN stated the data was not incorrect, but he believed the concentration of sebacate was too high. MARTONEN did not offer anyone who could support this claim initially. He subsequently stated Dr. MIKE SHEARER (919/515-3298), Professor, Department of Mathematics at North Carolina State University (NCSSU) and then NCSSU post-doctoral student REBECCA SEAGAL, who may now be in Bath, England, may support MARTONEN's recollection.

MARTONEN stated EPA was aware of the data from KIM's study because of daily reviews during KIM's experiments, prior to when the over-exposure of sebacate was discovered in August of 2001. MARTONEN acknowledged that although the data was available for review prior to August 2001, it did not mean the data calculations were made by EPA prior to August 2001 to

understand the connection of the over-exposure of sebacate. MARTONEN stated this was evidence of an EPA cover-up prior to 2001. MARTONEN stated further evidence of a cover-up was GILMAN's July 2004 letter to MARTONEN, in which GILMAN acknowledged that an over-exposure had occurred and listed action EPA had taken as a result. MARTONEN also stated since he did not know if letters were sent to the subjects informing them of the over-exposure, he did not believe they were notified. MARTONEN stated he wanted to see the letters informing the subjects of the overexposure. When told the subjects were notified, MARTONEN questioned the content of the letters and summarized what must have been their content as "trust me, I work for the government." MARTONEN stated the letters he sent to EPA Administrators were themed around the fact that the Human Studies Agreement Consent Forms were violated.

MARTONEN stated EPA employees MIKE DEVITTO and REX PEGRAM could also support his claim EPA knew of the over-exposure of sebacate prior to August 2001. MARTONEN recalled an incident prior to 2001, and believed it occurred in 1999 or 2000, when DEVITTO came into a break-room where MARTONEN was. DEVITTO stated "You're not going to believe what just happened," and that he had just returned from the University of North Carolina (UNC) and stated he had a conversation with BIRNBAUM in her office with Dr. HAROLD ZENICK. MARTONEN stated DEVITTO said the "shit hit the fan" because KIM's experiments revealed exposure of sebacate to subjects in excess of what they consented to receive had occurred. MARTONEN stated PEGRAM also heard this conversation.

MARTONEN continued to allege EPA was still covering-up the over-exposure of sebacate. MARTONEN stated this, despite the fact MILLER and an external peer review panel was contracted by EPA to review the matter and make recommendations, and that UNC officials outside of EPA were aware of the over-exposure and EPA's response to the over-exposure. MARTONEN again cited he did not believe EPA notified the subjects of KIM's study and they were all okay with the information. MARTONEN denied he ever spoke to any subject of KIM's study. MARTONEN stated GILMAN cited in his July 2004 response letter that the subjects had a "unanimous it was ok" view. MARTONEN stated he did not believe all the subjects thought it was okay.

MARTONEN denied he had any agenda to make these allegations. MARTONEN rated his cover-up allegation was of 99% importance and the over-exposure was at 1% importance.

MARTONEN acknowledged all scientists made experimental errors, and that was why he made the above ratings, because the cover-up of the errors was the larger problem.

When asked if he viewed the sebacate as a hazardous substance, MARTONEN stated "yes and no". MARTONEN acknowledged labs over the world were using it, but the toxic properties were unknown, as it depended on the dosage and the target organ. MARTONEN stated the sebacate was used as a control aerosol. MARTONEN suspected if ten physicians were questioned if sebacate was harmful, five would say it was and five would say it was not.

MARTONEN then stated Dr. JACKY ROSATI, now at EPA, was a post doctorate student during 2001. MARTONEN stated he was on her dissertation review committee. MARTONEN stated ROSATI could confirm KIM's study was known to EPA that over-exposures of sebacate occurred prior to 2001. MARTONEN stated ROSATI was conducting similar studies for KIM and used the same type of equipment as KIM's sebacate study. MARTONEN stated ROSATI was aware of KIM's experiments and conditions of over-exposure of sebacate prior to 2001. MARTONEN also stated Dr. JAMES BROWN may be aware of KIM's over-exposure. MARTONEN stated

ROSATI went to Dr. PHIL BROMBERG at UNC with her findings about August 2001. MARTONEN stated he did not understand the significance of making a distinction of if a cover-up occurred prior to or after August 2001.

MARTONEN stated after he began sending letters to EPA Administrators, Dr. REITER, ZENICK and BIRNBAUM started "hammering me". MARTONEN denied he had any other issues with BIRNBAUM. MARTONEN stated as a result of the allegations he made to OSC, he wanted BIRNBAUM, ZENICK, REITER and everyone involved with the cover-up terminated. MARTONEN stated if they were not terminated as a result of this investigation, he would take the allegations to the United Nations World Court, if he stayed healthy (he stated he had cancer surgery in November 2004). MARTONEN maintained the experiments were "Nazi-like". MARTONEN stated not getting a resolution of BIRNBAUM, ZENICK and REITER terminated would be "a bitter disappointment to me" that people have "conveniently forgotten". MARTONEN was unable to respond when told professional experts reviews of the raw data did not support MARTONEN's allegation.

MARTONEN stated if any witnesses he provided to support his allegations (SHEARER, SEAGAL, DEVITTO, PEGRAM, and ROSATI) did not support MARTONEN's allegations, then the witnesses had conveniently lost their memory or had to say MARTONEN was lying because of fear to keep their jobs with EPA.

MARTONEN stated he would prepare a signed sworn statement and notify reporting agent when it was ready. MARTONEN stated he was feeling sick from his cancer medication at this time and the interview concluded.

Attachment

1. Curriculum Vitae

CURRICULUM VITAE

Name:	Ted B. Martonen, Ph.D.
Home Address:	3109 Carriage Trail Hillsborough, NC 27278 (919) 644-1726
Business Address:	Immediate Office Mail Drop B-143-01 Experimental Toxicology Division National Health and Environmental Effects Research Laboratory U.S. Environmental Protection Agency 109 T.W. Alexander Drive Research Triangle Park, NC 27711 and Adjunct Professor Division of Pulmonary Diseases Department of Medicine University of North Carolina Chapel Hill, NC 27514 (919)-541-7875 martonen.ted@epa.gov
Education:	B.S. Applied Mathematics (1966), University of Michigan B.S. Engineering Mechanics (1966), University of Michigan M.S. Applied Mathematics (1971), Michigan State University M.S. Biophysics (1973), University of Rochester Ph.D. Biophysics (1977), University of Rochester
Scholastic Honors:	National Science Foundation Training Grant, 1969-71 National Institutes of Health Training Grant, 1971-77
Professional Awards:	Scientific and Technological Achievement Award (STAA) from the EPA Scientific Advisory Board: 1986, 1990, 1994, 1995, 1997 Smithsonian Institution Award in Medicine 1997 Fellow of the Wessex Institute of Great Britain 2003
Associate Editor:	Cell Biochemistry and Biophysics (International Journal, Humana Press) Advances in Computational Bioengineering (Textbook Series, WIT Press)
Editorial Boards:	Inhalation Toxicology International Journal of Particulate Science and Technology (Past) Journal of Aerosol Medicine (Past)
Professional Affiliations:	American Association for Aerosol Research International Association for Aerobiology Society of Toxicology International Society for Aerosols in Medicine

<p>Past Employment:</p>	<p>Research Scientist, 9/82-9/84 Northrop Services, Inc., Environmental Sciences Research Triangle Park, NC 27709</p> <p>Primary responsibility is the development of mathematical models that describe the fate of inhaled particulate matter in the respiratory systems of man (adults and children), and laboratory test animals used as human surrogates in inhalation exposure studies to assess potential hazards to human health from toxic airborne materials. Additional responsibilities include: the design and development of an artificial human thorax for use in experiments quantitating the hygroscopic growth rates of pollutant particles of health effects concerns, and fabrication of an experimental system utilizing replica casts of human lungs for use in aerosol deposition studies.</p>
	<p>Senior Research Scientist, 4/81-9/82 Inhalation Technology and Toxicology Section Battelle Pacific Northwest Laboratories Richland, WA 99352, and Associate Adjunct Professor Pulmonary Division, Department of Medicine University of California Irvine, CA 92717</p> <p>Project Coordinator, collaborative biomedical engineering research program assessing the fate of inhaled particles and gases in the human respiratory system</p>
	<p>personal technical responsibility is the design and development of a computer monitored drug delivery system utilizing transducer technology appropriate for respiratory therapy regimens. Project Manager, engineering program, "Monitoring of Airborne Contaminants from Coal Liquefaction Processes:" personal technical responsibility is the design and testing of instrumentation for real-time dosimetry of personnel exposed to ambient particulate matter and vapors of health effects concern. Principal Investigator, special studies project, "Development of Human and Laboratory Animal Aerosol Deposition Models:" objective is to develop computer programs to study factors affecting the behavior of airborne toxic materials in the respective respiratory systems "Q" level federal security clearance.</p>

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF TED MARTONEN

On May 12, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. TED MARTONEN (919/541-7875), National Health Environmental Effects Research Laboratory (NHEERL), in his office, RTF Building, room number 2134 at Research Triangle Park (RTP), NC. MARTONEN was known to the reporting agent and identification was not shown. The purpose of the interview was a follow-up to a previous interview to support an investigation of allegations made to the Office of Special Counsel (OSC) by MARTONEN, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

When asked to clarify how MARTONEN had access to review Dr. CHONG KIM's log books, MARTONEN stated Dr. LINDA BIRNBAUM, his supervisor, instructed MARTONEN to work with KIM to facilitate a collaboration between the two about 1997 or 1998. MARTONEN told KIM, MARTONEN wanted to see the log books related to KIM's sebacate study. MARTONEN said KIM told him he would not give the log books to MARTONEN. MARTONEN acknowledged it was common for a researcher not to give results related to a study they were conducting to others while the study was on-going. MARTONEN stated BIRNBAUM instructed MARTONEN to get the books from KIM. MARTONEN stated when he explained that to KIM, he produced the log books for MARTONEN to review.

MARTONEN stated he was directed a second time by BIRNBAUM about 1999 or 2000 to review KIM's log books. MARTONEN stated KIM gave him the log books when MARTONEN made the request. MARTONEN stated he told BIRNBAUM of the over-exposure of sebacate during his annual or semi-annual performance review, but did not document he told BIRNBAUM because she was his supervisor and he trusted her to do something with the information.

MARTONEN stated he did not speak to Dr. JAMES BROWN regarding when the first allegations came forward in 2001 of an over-exposure of sebacate to human subjects occurred with KIM's study. MARTONEN stated he had only spoken to Dr. JACKY ROSATI at that time,

Investigation Conducted on: May 12, 2005	Conducted at: Research Triangle Park, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 12, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>

because he was on her doctoral review committee. MARTONEN stated he had a meeting with ROSATI and her thesis advisor at the University of North Carolina, Dr. DAVID LEITH, because ROSATI questioned if she should continue to conduct research for KIM.

Related to a possible conflict with KIM, when KIM chose Dr. KLEINSTREUER of North Carolina State University over MARTONEN, he clarified he did not have any animosity towards KIM because he chose to work with KLEINSTREUER on a study. MARTONEN stated Dr. DEVLIN, KIM's supervisor, ordered KIM to make the change.

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF LINDA BIRNBAUM

On May 18, 2005, Special Agent's (SA) LEONARD O. NEWMARK, Desk Officer, Financial Fraud Directorate, and DAVID L. COTNER, Special Investigations Unit, interviewed Dr. LINDA S. BIRNBAUM, Division Director, Experimental Toxicology Division, Office of Research and Development (ORD), National Health and Environmental Effects Research Laboratory (NHEERL) at her office in Building B, Room #B141D, at the EPA Facility at Research Triangle Park, (RTP), NC. BIRNBAUM was shown proper identification by reporting agent. The purpose of this interview was to follow-up on information provided by TED MARTONEN, Research Physicist, RTP. BIRNBAUM provided the following information:

BIRNBAUM was asked if MARTONEN informed her prior to August 2001 regarding the dosing errors associated with the sebacate study performed by KIM. BIRNBAUM stated that she "does not know anything about this," and "that it is not true" that MARTONEN ever told her about the dosing errors prior to August 2001. BIRNBAUM stated MARTONEN's opinion that EPA knew subjects were being exposed outside of the approved protocols is "not true."

BIRNBAUM stated that there was another episode, a few years prior to 2001, in which KIM had allowed a human subject to participate in an experiment who did not meet the experiments' protocol requirements—this was a different experiment than the sebacate one. BIRNBAUM stated that KIM received an admonishment letter about this incident. BIRNBAUM stated that she was not aware of the sebacate dosing error until after being informed of this prior protocol deviation by KIM.

BIRNBAUM was asked if she directed MARTONEN to obtain KIM's log books on the sebacate experiment. BIRNBAUM stated that while she had repeatedly encouraged MARTONEN to collaborate with KIM, she "never told" MARTONEN to look at KIM's notes, obtain KIM's log books, or inform KIM to provide his log books to MARTONEN.

Investigation Conducted on: 05/18/05	Conducted at: Durham, NC
Conducted by: SA Leonard O. Newmark <i>L.O.N.</i>	OI File No: 2005-0002
Date Prepared: 05/19/05	Prepared by: LON <i>[Signature]</i>

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INTERVIEW OF LINDA BIRNBAUM

BIRNBAUM stated that KIM has no connection or association with pharmaceutical companies. BIRNBAUM stated that the issue of KIM's sebacate dosing errors may have been the result of "hubris" or "cultural differences." BIRNBAUM stated that KIM "never really thought about" the measurement changes and how this would impact the protocol of the experiment. BIRNBAUM stated that she also faults the former NHEERL division director for a lack of oversight. BIRNBAUM stated that every year KIM would submit protocols and that more intensive oversight would have caught the dosing errors. BIRNBAUM stated that prior to the incident, dosemetry studies had not received the same scrutiny as chamber studies. BIRNBAUM stated that currently this has changed and the protocol approval process has been strengthened.

BIRNBAUM stated that since sebacate is not a harmful substance, KIM paid less attention to protocol details.

BIRNBAUM stated that regarding the external review panel established to review this matter, she was "totally uninvolved," and she had no role in selecting panel members, did not know who was on the panel, and was not asked to speak to the panel.

BIRNBAUM stated that MARTONEN has a "vendetta" against her and he has alleged that all of his managers at EPA have been unethical. BIRNBAUM stated that MARTONEN is not emotionally stable and that approximately twenty years ago he had a serious medical condition and that a former fiancée of his committed suicide. BIRNBAUM stated that MARTONEN's behavior has been "unacceptable for years" but that she did not want to discipline him for fear of his reaction.

BIRNBAUM stated that MARTONEN's field of research has not had much impact on EPA and that MARTONEN, unlike other researchers in BIRNBAUM's group, rarely receives invitations to speak at conferences in which his expenses are paid by the sponsoring entity.

BIRNBAUM stated that MARTONEN is "jealous" of KIM because KIM had a laboratory and was allowed to conduct human experiments.

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**OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS**

INTERVIEW OF LAWRENCE REITER

On May 12, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. LAWRENCE REITER (919/541-2281), Director, National Health Environmental Effects Research Laboratory (NHEERL), in his office, Building B, room number C310 at Research Triangle Park, NC. REITER stated he had been the NHEERL Director for about ten years and employed by EPA since 1973. REITER was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

REITER stated he was informed by Dr. HAROLD ZENICK about the second day after the protocol violation of Dr. CHONG KIM's study was identified as over-exposing di-2-ethylhexyl sebacate (sebacate) to human test subjects in August 2001. REITER stated Dr. LINDA BIRNBAUM and Dr. ELSTON SEAL may have also been at the same meeting notifying REITER. REITER recalled he was briefed there may have been a violation, and further checking was required. REITER stated he agreed with ZENICK to stop KIM's study and directed it to happen. REITER stated the next step was to look at the records of the study and calculations and determine if a violation occurred and the extent of a violation. REITER stated determining that information was a prolonged activity. REITER stated he was informed of what was going on, but did not manage the review of KIM's study. REITER stated ZENICK, BIRNBAUM and SEAL maintained oversight of the Human Studies oversight protection.

REITER also recalled the Institutional Review Board (IRB) was immediately notified of the notification, though he could not recall within how many days the notification was made.

REITER also requested a vulnerability analysis of other protocol violations. REITER recalled data from Dr. FRED MILLER, who did an analysis of the over-exposure of sebacate of KIM's study, supported the test subjects were exposed to the sebacate at 30 - 50 times what the subjects consented to receive. MILLER stated he could not speculate on where the allegation of 100 times the consented exposure came from, but it was 'not based on data'.

Investigation Conducted on: May 12, 2005	Conducted at: Research Triangle Park, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 12, 2005	Prepared by: SA David L. Cotner <i>AM</i> <i>DL</i>

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REITER stated he suspected Dr. TED MARTONEN may have been the source of the allegation to OSC because of an Equal Employment Opportunity Complaint MARTONEN had against the EPA.

REITER stated there was no proper way that MARTONEN should have had authorized access to the logs from KIM's study. REITER stated MILLER and the external peer review panel would have had access to the logs.

REITER stated he could not see how there could have been a cover-up of KIM's sebacate study. If anything, REITER stated BIRNBAUM reacted as conscientiously and meticulously as could be expected. REITER's view was BIRNBAUM aggressively managed the over-exposure incident, including documentation and communications with the IRB.

REITER believed if KIM submitted a protocol amendment with a proposal of exposure of sebacate at the level that was actually given at the over-exposed level, the IRB would have approved the protocol. REITER stated KIM looked at the size of the particle deposition in the lung, not a cause and effect study. REITER asked 'what's to cover up? The problem was a protocol violation'.

REITER recalled a comment by one of the external peer review panel members who stated he couldn't think of an institution that would have acted as extensively as EPA did. REITER stated there was no way BIRNBAUM could have influenced the external peer review panel. To the contrary, REITER stated he believed the external peer review panel, if anything, would have been 'hyper-critical' because of the interest and integrity of the scientific community.

REITER stated NHEERL learned from KIM's over exposure of sebacate that NHEERL needed to have in place a culture and process which allowed safety and adherence to protocols to be a continual process. REITER stated that included on-going training and meetings. The philosophy NHEERL adopted after 2001 was vigilance to keep NHEERL employees informed so NHEERL could lower the chance of an accident happening. As part of that, REITER stated NHEERL conducts annual reviews of the human studies program to maintain that vigilance.

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**OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS**

RECEIPT OF DOCUMENTS FROM KAREN PALMER

On June 3, 2005, SA DAVID L. COTNER, Special Investigations Unit, reviewed a copy of a letter sent from Dr. TED MARTONEN to EPA Administrator CHRISTINE T. WHITMAN. The letter was one letter from a package of letters received from KAREN PALMER (919/541-7837), Attorney, Office of General Counsel. PALMER gave the package of letters to the reporting agent on May 3, 2005. The entire package is described in a separate EPA Form 2720-15.

The purpose of reviewing the letter was to support an investigation of allegations made by MARTONEN of alleged misconduct by CHONG KIM, where MARTONEN alleged EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of KIM.

The attached letter dated January 31, 2002 (Attachment 1) is the earliest letter referencing Dr. KIM's study.

Attachment

1. Letter from MARTONEN to WHITMAN, dated January 31, 2002

Investigation Conducted on: June 3, 2005	Conducted at: Washington, DC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: June 3, 2005	Prepared by: SA David L. Cotner <i>DLC</i>

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

DATE: January 31, 2002

TO: Christine T. Whitman, Administrator
U.S. EPA
Mail Code 1101A
Ariel Rios Building
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

FROM: Ted Martonen, Ph.D.
Senior Research Scientist
Mail Drop 74
ETD, NHEERL
U.S. EPA
Research Triangle Park, NC 27711

A handwritten signature in black ink that reads "T Martonen".

SUBJECT: Cover-Up of Unauthorized U.S. EPA Human Subject Experiments

It is my duty as an American citizen and an employee of the U.S. EPA to inform you that the health and rights (civil, medical and legal) of innocent human subjects have been compromised by the actions of senior management of the National Health and Environmental Effects Research Laboratory (NHEERL). The innocent people have been, and are continuing to be, treated as guinea pigs. They must be protected.

In my six-page, single-spaced letter to your office dated December 12, 2001, I described the dangerous environment created within the U.S. EPA by the senior management of NHEERL. The specific topics that I documented were: [A] Verbal abuse, [B] Discrimination, [C] Unjust treatment, [D] Unfair demands, [E] Unsafe management practices, [F] Discrimination, [G] Mistreatment of student, [H] Mistreatment of student, [I] Discrimination.

[5.] **Violation of Memorandum from the Agency Human Research Subjects Review Official.** Research with human subjects cannot be conducted without the written approval of the designated official. The memorandum is based on information provided in the aforementioned SOP, IRP, and IRB application, and may be titled "Protection of Human Subjects Certification".

[6.] **Violation of Consent to Participate in a Research Study (CPRS) Form.** Studies with human subjects require that the subjects be informed of the specific experimental conditions, consent to them, and sign a CPRS form. The CPRS form of record was not suitable for the studies performed. That is, the experimental conditions to which the human subjects were actually exposed were not those described to them. To be succinct, the tests performed on them were not the tests that they had agreed to when they signed the CPRS forms.

I will now summarize the critical points. The necessary documentation (points 2-5, above) describing the scientific, technical and administrative aspects of the human subject investigations were not appropriate for the experiments actually conducted in the HSD (Dr. Linda Birnbaum, Acting Director). Clearly, this is unconscionable behavior for an institution of the federal government, especially the U.S. EPA whose avowed mission is to protect human health. What is truly abhorrent, however, is that after the human subjects signed the CPRS forms (point 6, above) the experimental conditions were changed without informing them. Moreover, senior NHEERL management have still not informed (point 1, above) the human subjects of the unauthorized experiments. Obviously, points 1 and 6 may be particularly troublesome to the federal government *per se* and especially the U.S. EPA from civil, medical and legal rights perspectives.

The ongoing cover-up by senior NHEERL management is an extremely dangerous path that puts all federal government research programs using human subjects at risk. The seriousness of this situation cannot be overemphasized: to be candid, human subjects have been used, and are continuing to be treated as guinea pigs. This situation has the potential of blowing the lid off human subject research. The behavior of senior NHEERL management is incomprehensible; but, I have already alerted your office to it in my aforementioned letter of December 12, 2001.

For the good of all federal government research, your office must now act quickly and decisively. The correct starting point for the U.S. EPA would be to follow the six-step procedure outlined below:

- immediately notify (in writing) the human subjects involved;
- inform them that their civil, medical and legal rights were violated;
- admit wrongdoing;
- beg forgiveness;
- allow the human subjects to take appropriate actions following consultations with their

Because of the nature of this memorandum, copies of this letter are being sent to Mr. F. James Sensenbrenner, Jr. (Chairman, Committee on the Judiciary, US House of Representatives) and Mr. Sherwood L. Boehlert (Chairman, Committee on Science, US House of Representatives).

This letter is being sent by Federal Express with tracking number 834063185897.

cc: Mr. F. James Sensenbrenner, Jr., Chairman, Committee on the Judiciary, US House of Representatives
Mr. Sherwood L. Boehlert, Chairman, Committee on Science, US House of Representatives

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**OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS**

INTERVIEW OF TED MARTONEN

On May 18, 2005, SA DAVID L. COTNER, Special Investigations Unit, and SA LEONARD NEWMARK, Financial Fraud Directorate, interviewed Dr. TED MARTONEN (919/541-7875), National Health Environmental Effects Research Laboratory (NHEERL), in his office, RTF Building, room number 2134 at Research Triangle Park (RTP), NC. MARTONEN was known to the reporting agent and identification was not shown. SA NEWMARK displayed proper identification. The purpose of the interview was a follow-up to a previous interview to support an investigation of allegations made to the Office of Special Counsel (OSC) by MARTONEN, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher. MARTONEN also provided a signed, sworn written statement (Attachment 1).

MARTONEN provided an overview of what he discussed during previous interviews by reporting agent. MARTONEN clarified what he meant in his allegation when he questioned what other dangerous substance EPA was testing in Dr. CHONG KIM's di-2ethylhexyl sebacate (sebacate) study. MARTONEN stated he questioned other EPA studies in general. MARTONEN acknowledged there were no other substances tested by KIM's study. Rather, MARTONEN suggested, because of KIM's study, other EPA studies of cigarette smoke, auto exhaust, asbestos, diesel exhaust, ammonium sulfate, etc., may have testing protocol issues because of the over-exposure of sebacate to subjects of KIM's study. MARTONEN questioned if the methodology was flawed in one study (KIM's), was the methodology of other studies flawed too?

MARTONEN referred to another study done by a post-doctorate student under Dr. REX PEGRAM, EPA, who made a mistake of calculation, which led to an over-exposure of another substance. MARTONEN acknowledged it was the other study reviewed by the Human Subjects Review Panel (HSRP) which also reviewed KIM's sebacate study. MARTONEN stated the difference was EPA management, at the presentation to HSRP, used the study of PEGRAM's doctoral student and explained actions taken to correct the cause of that over-exposure, then quickly by-passed the presentation of KIM's study, stating it was the same as the first study

Investigation Conducted on: May 18, 2005	Conducted at: Research Triangle Park, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 18, 2005	Prepared by: SA David L. Cotner <i>DLC</i>

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presented. MARTONEN stated that was told to him by PEGRAM and Dr. MIKE DEVITO, EPA.

MARTONEN stated he used the number one hundred times what the subjects consented to receive in his allegation because it was a magnitude of the second order. He stated, as a scientist, that was how he remembered things. MARTONEN stated he could not recall the actual amount of the over-exposure he saw in KIM's log books. MARTONEN stated it could have been "67.1 or 113.4".

MARTONEN again stated he spoke to JACKY ROSATI, EPA, before August 2001 about the over-exposure of sebacate to human subjects. MARTONEN stated to the best of his knowledge, it was before August 2001 when ROSATI discovered the over-exposure of sebacate. MARTONEN stated it could have been up to a year before and speculated ROSATI was aware of the over-exposure of sebacate and may have not made any notifications about it for up to a year. MARTONEN stated he was aware of it from discussions with ROSATI and her Thesis Advisor, DAVID LEITH. MARTONEN stated he recalled the discussions because he was on ROSATI's Doctoral Committee.

MARTONEN again advised Dr. MICHAEL SHEARER and his doctoral student at the time, REBECCA SEAGAL, could also support his assertion that others new of the over-exposure of sebacate prior to August 2001. MARTONEN stated he would not be surprised if SHEARER could not recall the conversation because it happened about eight years earlier.

MARTONEN was advised some of the people he stated could support his belief EPA knew of KIM's over-exposure of sebacate prior to August 2001 did not recall the same timeline. MARTONEN stated if they didn't recall the over-exposure of sebacate prior to August 2001, their memories could have faded to those details, or he suggested of the EPA employees, EPA management may have threatened them. When asked for specific information that EPA employees may have been threatened or intimidated, MARTONEN admitted he could not provide details and that was speculation on his part.

MARTONEN again stated he looked at KIM's log books before August 2001, and stated as proof the fact of the two articles he published prior to 2001 with KIM. MARTONEN stated he was truthful and had not perjured himself. MARTONEN stated his statement was the written truth as he knew it. MARTONEN stated he wanted to hold the people responsible accountable and wanted them fired, specifically mentioning Dr. LINDA BIRNBAUM, Dr. HAL ZENICK, and Dr. LARRY REITER. MARTONEN stated, despite his health, if this investigation did not substantiate his allegations, he would take the matter to the United Nations and the World Court.

Attachment

1. Signed, sworn statement, dated May 18, 2005

STATEMENT

City: RESEARCH TRIANGLE PARK Date: MAY 18, 2005

State: NC Time: 3:00 PM

I, TERRY BLAYNE MARTONEN, PH.D.
(Name) (Title)

EO, ETD, NHEERL, USEPA, residing at 3109 CARRIAGE TRAIL,
(Organization) HILLSBOROUGH, NC 27278, hereby make the following statement before

Special Agent(s) DAVID L. COTWER and Leonard Neumann

of the Office of Inspector General, United States Environmental Protection Agency. TBM x 05/18/05
See Attached 13 page schedule

T B Martonen

Attachment (1)

TBM 1 of 2 files



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

DATE: May 13, 2005

TO: David L. Cotner, Special Investigations Unit, Office of Inspector General (OIG), 1200 Pennsylvania Avenue (NW), Washington, DC 20460

FROM: Ted Martonen, Ph.D., Senior Research Scientist, IO/ETD/NHEERL/USEPA

T Martonen

SUBJECT: Written statement describing illegal human subject experiments and the ongoing cover-up by USEPA management and administration

This requested written statement follows our discussion on Wednesday, May 11, in the presence of Jerry L. Polk, OIG/USEPA. This material is not submitted as a stand-alone document. Rather, it is intended to augment the correspondence I have already submitted directly to former and present EPA Administrators:

- Christine Whitman;
- Mike Leavitt; and,
- Stephen Johnson.

The point of this written statement is to provide "glue" (i.e., your term), to the extent possible, of the material in the aforementioned communications.

To begin, I must put matters into proper perspective. I ask for your patience and understanding while I present support material. This is extremely important because this is an official government communication on USEPA letterhead and, as you clearly emphasized, the matter being investigated is criminal not civil. Also, I have learned that a document submitted for one purpose can easily be used for another purpose; hence, it is prudent to be as complete as conditions permit.

I have pursued this matter of illegal human subject experiments for several reasons, the key ones being:

- (A) the individuals whose human subject consent forms were violated have a right to be informed of the transgressions;
- (B) the parents of the test subjects have a right to be informed of what was done to their children;
- (C) the federal government must take strong disciplinary action against those government employees involved in the performance of the illegal experiments;

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(D) the federal government must take strong disciplinary action against those government employees involved in the initial, and continuing, cover-up of the illegal experiments; and,

(E) I must protect myself.

Regarding (A-D), I have always been driven by my belief that the US government must protect, and be accountable to, its citizens. Now, as a cancer patient, the sanctity of human life and well being has been impressed on me even more than when I began this process. Regarding (E), it must be noted that I have been abused and harassed in the federal government workplace by EPA management and administration since I have documented the illegal human subject experiments and their ongoing cover-up.

Regarding (E) of the preceding paragraph, it must be emphasized that the behavior of certain members of USEPA management and administration, namely:

- Dr. Linda Birnbaum (Director, Experimental Toxicology Division (ETD), National Health and Environmental Effects Research Laboratory (NHEERL));
- Dr. Hal Zenick (Associate Director for Health, NHEERL); and,
- Dr. Larry Reiter (Director, NHEERL),

have caused stress, tension and anxiety. As I have documented to EPA Administrators Whitman, Leavitt and Johnson, they have acted in concert, and by design, to adversely affect my health. Their collective behavior has constituted discrimination by reprisal, and is an element of my Office of Civil Rights (OCR) and Equal Employment Opportunity Commission (EEOC) cases against the USEPA. The seriousness of the matters is such that the OCR/EEOC cases will be addressed in a trial in Federal Court scheduled for June 07-09, 2005.

[1.] The prime source of the glue will be the log books for the human subject experiments performed by Dr. Kim of the Human Studies Division (HSD)/NHEERL/USEPA. The USEPA is required to record experimental conditions and maintain and store such log books. A salient issue is that the log books are routinely examined and reviewed in a timely manner during tests. Therefore, USEPA management and administration cannot deny being responsible for the contents of the log books and the experiments *per se*. Regarding the relevance of the log books and their recorded information to the date of August 2001 (which you have been erroneously informed is germane by USEPA management and administration), see factor [10.] below.

The log books must identify and quantitate the aerosols administered to the subjects. For instance, the toxicological nature of the substances administered to the human subjects must be acknowledged and the aerosol doses delivered to the human subjects must be known in terms of the aerosol masses deposited within their respiratory systems. The seminal point is that the experiments cannot violate the consent forms signed by the human subjects prior to the experiments. This fact must be emphasized: whatever the agreed concentrations were, they could not have been exceeded. It would have constituted a heinous violation of human subject testing.

All of the information that you need is in the USEPA log books. Obviously, they are official US government documents. From a scientific perspective, the log books would have to

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be the keystone to any legal proceeding.

[2.] **The experiments were conducted in the Center housing the HSD on the UNC campus.** Among the individuals in the Center who discovered the experiments were Jacky Rosati (i.e., a Ph.D. student) and James Brown (i.e., a Post-Doctoral Trainee). At the time I was a member of the doctoral committee of Ms. Rosati, and she told me that they reported the subject matter to Philip Bromberg, MD (i.e., Professor of Medicine, UNC). Consequently, I had discussions about the subject matter with Ms. Rosati and her Thesis Advisor, Professor David Leith.

The aforementioned individuals can offer their own testimony as to their respective involvements and time scales. For example: who knew what and when?

[3.] Let us consider the following manuscript: Segal R.A., Martonen T.B., and Kim C.S. Comparison of computer simulations of total deposition to human subject data in healthy test subjects, J. Air & Waste Manage. Assoc. 50: 1262-1268 (2000). The object of the manuscript was to foster collaboration within the NHEERL, particularly between the ETD in RTP and the HSD in Chapel Hill. I was explicitly directed to contact Dr. Kim to initiate the work by Dr. Birnbaum.

The salient point is that the manuscript was published in 2000. Due to research, writing, reviewing and publishing times, that work was done about 2-3 years before; say, 1997-98. **This is irrefutable and unambiguous proof that the USEPA management and administration had knowledge of the work before August 2001. As mentioned previously, you have been misled by USEPA management and administration to believe that the date is relevant, but it is not; please see factor [10.], below.**

Indeed, to establish a firm time line, the date during which the manuscript went through mandatory internal USEPA clearance can be determined by an OIG investigation. At the conclusion of the internal review process, Dr. Birnbaum, as my supervisor, would have had to sign off on the manuscript before it could have been submitted.

To conduct the research, I (i.e., as the EPA person doing the modeling) had to see Dr. Kim's log books for the human subject experiments. Following inspection of the log books, I realized that the concentrations of inhaled aerosols were very high. When I raised the issue with Dr. Kim, he said the concentrations were OK otherwise the work would not have been approved by the UNC/EPA Human Subject Review Committee, and I had no reason not to believe him.

I raised the issue of the seemingly high concentrations with Dr. Birnbaum on two occasions, during my annual and mid-year reviews, but was told that the work had been approved by the Human Subject Review Committee, so that it was OK. Now, I wish I had been more persistent; of course, hindsight is 20/20.

[4.] Now, let us address another manuscript: Segal, R.A., Martonen, T.B., Kim, C.S., and

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Shearer, M. Computer simulations of particle deposition in the lungs of chronic obstructive pulmonary disease patients, *Inhal. Toxicol.* 14: 705-720 (2002). Again, due to research, writing, reviewing and publishing times, that work was done about 2-3 years before; say, 1999-2000. **Again, this is irrefutable and unambiguous proof that the USEPA management and administration had knowledge of the work before August 2001. Again, you have been misled by USEPA management and administration to believe that the date is relevant, but it is not; please see factor [10.], below.** Again, to conduct the research, I (i.e., as the EPA person doing the modeling) had to see Dr. Kim's log books for the human subject experiments. Again, following inspection of the log books, I thought that the concentrations of inhaled aerosols were too high. Again, when I raised the issue with Dr. Kim, he said the concentrations were OK otherwise the work would not have been approved by the UNC/EPA Human Subject Review Committee, and I had no reason not to believe him.

Again, I raised the issue of the apparently high concentrations with Dr. Birnbaum on two occasions, during my annual and mid-year reviews, but was told that the work had been approved by the Human Subject Review Committee, so that it was OK.

Again, it would be a straightforward matter for the OIG to fix a clear time line on the involvement of USEPA management and administration. Remember, at the conclusion of the required internal review process, Dr. Birnbaum would have had to sign off on the manuscript before it could have been submitted.

[5.] I also received information about the illegal human subject experiments directly from Mike DeVito, Ph.D. At the time, Dr. DeVito was a Post-Doctoral Trainee under Dr. Birnbaum, who was serving as Acting Director, HSD. Currently, Dr. DeVito is a Branch Chief in Dr. Birnbaum's ETD.

Rex Pegram, Ph.D., was present when Dr. DeVito revealed the exposure of the illegal human subject experiments. Dr. Pegram was at the time, and still is, a scientist in Dr. Birnbaum's ETD; indeed, Dr. DeVito is his first line supervisor (i.e., Branch Chief). Dr. DeVito told us of the discussions that he had witnessed, and sometimes participated in, between Drs. Birnbaum and Zenick. The discussions took place in Dr. Birnbaum's office in the HSD in the Center on the UNC campus.

Dr. DeVito informed us that Dr. Bromberg of UNC had been informed of the experiments done by USEPA staff in his Center, and that he was "very angry".

[6.] During our lengthy discussion, you asked me whether or not Fred Miller, Ph.D., would qualify as a reviewer of the log books. I replied: "No". The straightforward reason being simply that Dr. Miller formerly had Dr. Birnbaum's position and could be considered, therefore, to be too close to the laboratories and individuals involved. Indeed, if I recall correctly, when Dr. Miller was here, the current ETD and HSD were separate parts of a mega-division termed the Inhalation Toxicology Division. Hence, he had a considerable job. I respect him as a scientist,

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but I truthfully believe that it (i.e., his involvement) would put him between a rock and a hard place. In short, it would have put him in the unenviable position of declaring that his former employees had violated the most sacred of codes, the human subject consent form. Therefore, if the position had been offered to him, I would have hoped he would have recognized that he was being manipulated by the management and administration of the USEPA, that there was clear conflict of interest, and that the very appearance of an impropriety would have done irreparable damage to any investigation. **For instance, an impartial investigator could easily claim a government "white-wash".**

That situation would have been tantamount to when the tobacco industry attempted to prove that cigarette smoking did not cause cancer by bringing in experts, whose past and/or current research was supported by the tobacco industry, to testify before the US Congress on their behalf.

[7.] **The issues of the magnitudes of the doses delivered to the human subjects is a "red herring" that has been skillfully used by USEPA management and administration to lead investigators astray.** They have claimed that the doses administered did not exceed by too much those agreed to by the test subjects in their consent forms. But, if the doses administered by the USEPA to the human subjects exceeded the consent values by a factor of 2 or 100 is not relevant. That is not the point, the point is this: a violation is a violation, period.

[8.] Another "red herring" used by USEPA management and administration is their claim that sebacate is not toxic. That argument of USEPA management and administration is false for two reasons.

- First of all, I have performed a review of toxicological studies and have determined that some authors have stated that the toxicological properties of sebacate are "unknown". My Attorney has the data.
- **Secondly, whether sebacate is toxic or not, is not the seminal issue in the USEPA studies. Here, the sanctity of the human subject consent form must be acknowledged. The real point is this: if a human subject consents to one corn flake, you cannot administer two corn flakes. The toxicity of corn flakes *per se* is not the issue, the issue is that you cannot violate the human subject consent form. I do not comprehend why the USEPA cannot recognize this fundamental fact.**

[9.] An issue that you introduced at the conclusion of our discussion on Wednesday, May 11, was this: what would I do in the future, if anything, if the investigation did not turn up evidence to support my case? I have given the matter thought, and I stand by my initial answer. If my health permits, I intend to fight for the truth. Someone has to fight for the little innocent people, and I guess it will have to be me. I did not ask for the job, it has found me. Clearly, I will have to use a different forum. **Either the**

- **World Court, or**
- **United Nations**

seem to be appropriate at this time. For your information, THE STATUTE OF THE WORLD

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COURT OF HUMAN RIGHTS is at <http://www.worldgovernment.org/wsalstat.html>. As of this date, I have not contacted either the World Court or the office of Secretary General Kofi Anan at the UN. I am sincerely hoping to have this matter handled by your office and within USA borders.

At this juncture, it should be noted that my Attorney (Mr. John Loftin) attempted to have the matter of illegal human subject experiments and my related discrimination by reprisal to be addressed in my aforementioned OCR/EEOC cases against the USEPA. However, Ms. Karen Palmer of the OGC wanted the matter to be treated separately. Why? I do not know. So, the current situation is the USEPA's own doing.

David, regarding factor [9.] the simple truths are outlined here. The US government was involved with the following situations.

- **The Tuskegee Study.** When it was exposed, people said "Never Again".
- **The Abu Ghraib Scandal.** When it erupted, people said "Never Again".
- **The American Citizen tests.** Now, the USEPA has used its own citizens as guinea pigs.

The most obvious elements these events have in common include the following, which are of fundamental importance:

- **US federal government employees (civilian/military) were involved;**
- **US federal government facilities (civilian/military) were involved; and,**
- **American Flags were flying over the people and buildings in which the events occurred.**

It would seem that a culture of human subject abuse and acceptance has crept into US government institutions, and that is frightening. I will pose a question to you: When does "Never Again" really mean "Never Again"? Someone has to stand up and hold the US government accountable, and I suppose it will have to be me. Do I expect to win? Perhaps not, it is simply that to do battle is the only honorable course of action. It is just something I cannot walk away from and hold my head up. If I die from the cancer I am currently fighting, I do not want to be on my death bed and think that I let innocent people suffer. The sad thing is this: When I originally revealed the situation directly to EPA Administrator Christine Whitman, I respectfully pointed out to her the proper course of action. It was to admit wrong doing and ask for forgiveness. But, she ignored me. Also, I informed EPA Administrator Mike Leavitt, and he ignored me. Now, EPA Administrator Stephen Johnson may ignore me. All he has to do is hold EPA management and administration accountable. Will he do it? Does EPA Administrator Johnson have the courage to do the right thing?

[10.] As I understand the situation (i.e., as you intimated), it is a critical contention of the USEPA that they were first informed of the illegal human subject experiments in August 2001. This is not true. I have established this in factors above; for examples, see factors [1.], [3.] and [4.].

The position of the management and administration of the USEPA is disingenuous. They seem to be implying that because they had discussions (i.e., internally and/or with outside

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consultants present) in August 2001, there was no cover-up after that time. That is, it is their contention that the meetings *per se* (e.g., as described in the letter from Dr. Paul Gilman, former head of the Office of Research and Development (ORD), now in my Attorney's possession), mean that there was no cover-up. Clearly, that reasoning defies logic. It is pure bureaucratic mumbo-jumbo.

David, consider the following scenario: Two criminals rob a liquor store, discuss it between themselves, then conclude: Well, we talked about the robbery, so it is not a crime. That is what the USEPA is saying: We have discussed the illegal human subject experiments, so they are OK. That attitude, of course, shows contempt for the American Public, whose children were used as guinea pigs (i.e., the fact that the students were of legal age is something you can argue with their parents). It is more reasonable to interpret the intent of such closed-to-the-public meetings as constituting stonewalling to preserve the *status quo*.

Such discussions (i.e., internal and/or with outside consultants present) among those actually responsible for the illegal experiments do not constitute disclosure. In fact, until full disclosure is made by the US government to the people used as guinea pigs and their parents, such internal discussion can, in fact, be regarded by the American Public as elements of an evasive process.

To be candid the date of August 2001 is a sham simply because the cover-up is continuing to this day (i.e., May 13, 2005). It will continue until the federal government properly notifies the subjects and their families of the facts surrounding their illegal experiments so that they can make informed decisions about how to proceed (e.g., legally and medically) after being informed that were used as guinea pigs and that the management and administration of the USEPA have continued to cover it up.

[11.] David, I have information of special importance to submit to you, as an individual who has served in the military, because on several occasions you asked if I had documentation, etc., and I explained that I took verbal instructions (i.e., orders) from my supervisors. Last evening (May 12, 2005) I watched Nightline on ABC and Ted Koppel interviewed Col. Janis Karpinski of the US Army Reserve. She was the commandant of Abu Ghraib prison where the scandal took place. Ted Koppel asked her this question: Colonel, you have been in the military for over 20 years, why didn't you put things in writing? Her response was: With hindsight, I should have. She explained that, in the military, one followed orders, so when military intelligence (MI) officers came and took over Abu Ghraib prison, she took verbal orders, stepped aside, relinquished command to MI, and did not document her concerns. Now, she is being hung out to twist in the wind. [Note - Col. Karpinski was a Brigadier General until her demotion a few weeks ago.]

I must ask you: do you ask your supervisor to put each instruction to you in writing? I cannot imagine the situation where you would say: Sir, kindly put that in writing because in 5 or 10 years I may have a law suit against you and I need a paper trail to use against you. In any event, how could you predict the future? Do you trust your boss?

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[12.] David, this is a simple case. Right is right, and wrong is wrong. Some salient facts for you are listed below.

- **Once the human subject consent forms were violated, the subsequent experiments *per se* were illegal. Accordingly, those involved should be terminated by EPA Administrator Stephen Johnson.**
- **Once the management and administration of the USEPA became aware, and did not immediately inform the human subjects that their consent forms were violated, the cover-up *per se* was in effect. Those involved should be terminated by EPA Administrator Stephen Johnson.**

The USEPA has attempted to mislead others with "smoke and mirrors". I have provided some explicit examples of their clumsy attempts above; see factors and [7.], [8.] and [10.]. Please, do not be lead astray. Whether the ethical, medical and legal rights of those innocent people used in experiments (and the rights of their loved ones) are protected or not, is now in your hands.

[13.] **The information you seek may be in the official Report of Investigation (ROI) compiled by the investigating authority who wrote the ROI on which my OCR/EEOC complaints have evolved successfully into the forthcoming Federal Court trial on June 07-09. My Attorney has the ROI.**

[14.] In courtesy to you, I have tried to be as complete as possible. However, I must be candid and admit that, as a cancer patient, I do not have my former energy. Perhaps I will be able to locate material in the future because, as you may not be aware, I was forcibly moved to this location by Dr. Zenick. This has resulted in the two points listed below.

- The crates you noticed in my office have not yet been unpacked. Of course, I have requested assistance from Dr. Zenick but he has denied it. This is, of course, merely another act of harassment from USEPA management and administration because I am trying to protect the innocent human subjects used as guinea pigs.
- Also, it must be noted that, to the best of my knowledge, not all of the material from my former office, work space, and laboratory have been moved. Hence some of the material that you want may be there. Can you, as part of your investigation, gain access to it?

The disturbing thing to me is that I have written twice to the new EPA administrator Stephen Johnson about this situation, and he has done nothing. Dr. Zenick has interpreted Mr. Johnson's inaction as official approval to continue harassing a cancer patient in the USEPA workplace.

[15.] All human subject experiments are closely monitored by the Quality Assurance (QA) officer in charge of the work. I would suggest, therefore, that you interview the QA officer in charge of the HSD to gain access to all of the human subject protocols.

[16.] Please refer to factor [9.] that I outlined previously. What I would submit to the World

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Court or United Nations would emphasize, but not be limited to, material shown below in factors [17. - 20.]. To be succinct, the significance being given by your office (i.e., the OIG) to the August 2001 date is not appropriate. It is a "smoke and mirrors" trick of USEPA management and administration. The deception is ongoing, as of today.

[17.] I am going to address the August 2001 issue again, because it is obvious that the USEPA is attempting to escape bring held accountable to the American Public.

Allow me to be clear: it was the responsibility of Drs. Birnbaum, Zenick and Reiter to know what was going on in the HSD of the NHEERL at all times. The USEPA is attempting to say that because meetings were held on August 2001 (i.e., when, you have told me, they have claimed to first become aware of the illegal human subject experiments), they are not responsible for anything done before that date because they tried to correct the situation after that date. That is twisted, and false, reasoning. What were Drs. Birnbaum, Zenick and Reiter doing: Sleeping at their desks while drawing US government salaries?

Drs. Birnbaum, Zenick and Reiter are responsible for all of the human subject experiments conducted within the HSD of the NHEERL since they held their respective positions in the US federal government.

[18.] It is the responsibility of the EPA Administrator Stephen Johnson to remember the following facts:

- Dr. Birnbaum served as the Acting Director, Human Studies Division (HSD), National Health and Environmental Effects Research Laboratory (NHEERL), and is now serving as Director, Experimental Toxicology Division, NHEERL;
- Dr. Zenick is still serving as the Associate Director for Health, National Health and Environmental Effects Research Laboratory (NHEERL); and,
- Dr. Reiter is still serving as the Director, National Health and Environmental Effects Research Laboratory (NHEERL).

In the preceding material, I have intentionally presented names, official US government job titles and official US government positions in bold, large font and have underlined critical information. I have a question for the EPA Administrator Stephen Johnson: Given their official positions and responsibilities within the US government, how can Drs. Birnbaum, Zenick and Reiter NOT be held accountable for the illegal human subject experiments?

[19.] It will be clear to the international community, after digesting the material presented above, that Drs. Birnbaum, Zenick and Reiter are no more than common school yard bullies. Unfortunately, their abusive behavior has not been corrected by their superiors. Taken with the material given in this document, the aberrant actions of USEPA management and administration will present an accurate and disturbing picture of conditions involving human subject abuse, the sponsorship of that abuse, the acceptance of that abuse, and the cover-up of that abuse. That is why I have been trying for years to have the EPA Administrators handle this matter "in house". But, EPA Administrators Whitman and Leavitt have ignored the situation until they could resign and/or get a promotion. The critical questions now is: What will the new EPA Administrator Stephen Johnson do? Will he take corrective action and terminate the employment of Drs. Birnbaum, Zenick and Reiter? Or, will it take the involvement of outside, impartial international authorities (e.g., the World Court) to correct the human subject abuses imposed on American Citizens by its own government?

[20.] Please refer to factor [13.] where the ROI was introduced. In it, the fact that an actual "ghetto" (i.e., the term used in the ROI) existed in the new USEPA building in spaces under the control of Dr. Birnbaum was documented.

In the text above and factors [1.] - [20.], I have attempted to provide glue. I have done so in a forthright manner. To the best of my knowledge, the information is correct. I submit it in good faith. My intent is to protect the innocent victims, and their loved ones, who have been mistreated in human subject experiments being covered up by USEPA management and administration.

In closing, I request the right to submit supplementary material in the future. **However, in fact, the bottom line is this: everything that you and the OIG will need to get to the bottom of this matter is in the USEPA log books. I have seen them and they are the "smoking gun".** Of course, when you read the log books you will see not only the recorded data *per se*, but also the comments written by USEPA management and administration during their review and examination. For instance, when I saw the log books related to the two manuscripts discussed in factors [3.] and [4.] above, I observed margin comments in different colored ink than the data and different handwriting than the recorder (i.e., Principal Investigator). Perhaps you can use that information to track down who knew what and when.

cc: John Loftin, Attorney, 117 North Churton Street, Hillsborough, NC 27278

TBM 05/18/05

TBM MANMOMEN

I have read the above statement, consisting of 2 pages. + 10 Page Attachment. x TBM,
I have initialed all pages and corrections to this statement.

I do solemnly swear (or affirm) that the information I have provided in this statement is the truth,
the whole truth, and nothing but the truth, so help me God. This I declare under the penalty of perjury.

TBM MANMOMEN

Maker's Signature

Subscribed and sworn to/affirmed by SA DAVID L. LOYNER before
me

at RESEARCH TRIANGLE PARK, NC (ROOM 2134, RTF)

this 18 day of MAY 2005

[Signature]
Special Agent

Witnessed by:
[Signature]
Special Agent

TBM x 2 of 2 plus
10 page Attachment

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF STEVEN BERNARD

On May 10, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. STEVEN BERNARD (919/966-1344), Chair, Institutional Review Board (IRB), University of North Carolina (UNC) at a conference room in Building # 52, UNC, Mason Farm Road, Chapel Hill, NC. BERNARD was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

BERNARD stated he was the Chair of the IRB and an employee of UNC, that oversaw Dr. CHONG KIM's study prior to the hang of the study in 2001 due to over-exposure of di-2-ethylhexyl sebacate (sebacate) given to human test subjects in August 2001. BERNARD's position as Chair of the IRB's was an appointed position during July 2000 by the Dean at UNC. BERNARD described Dr. DAN NELSON's responsibility as the Director of the IRB as administrative in nature, responsible for the day to day operations. BERNARD stated his position as chair focused on 'full board meetings'. BERNARD stated the IRB's were required to review studies once per year and often reviewed a series of amendments to a researcher's study.

BERNARD recalled from reviewing KIM's study, the original proposal had a specification that subject's would receive 50 micrograms of sebacate. BERNARD stated the subjects may have actually received about a 30 fold increase of sebacate to what they consented, or about 1.5 milligrams. BERNARD stated EPA used Dr. FRED MILLER's review as the basis of their findings to determine the amount of sebacate the subjects actually received. BERNARD considered MILLER an expert with a reputation of being very conservative in his reviews. BERNARD stated MILLER used a base-line that was a worse case scenario, because he could not establish a base-line from KIM's study as a starting reference point. Using the worse-case scenario by MILLER, BERNARD believed the figures MILLER provided of 30 - 50 times over-exposure of sebacate to what the subject's consented was accurate. BERNARD referenced his file and stated Dr. SEAL of EPA at the time told him the over-exposure amount was 30 times what the subjects consented to. BERNARD could not see how an allegation of 100 times

Investigation Conducted on: May 10, 2005	Conducted at: Chapel Hill, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 10, 2005	Prepared by: SA David L. Cotner

consent of the subjects could happen, based on MILLER's review.

BERNARD did not believe there was a cover-up to the inquiry into KIM's study. BERNARD stated SEAL 'bent over backwards' to send materials to the IRB. BERNARD rated EPA's role in the inquiry as a ten, and attributed the forthcoming of SEAL. BERNARD identified a one would have been a cover-up and a ten was a model of openness. BERNARD did not believe anyone, including Dr. LINDA BIRNBAUM, was involved in a cover-up related to the review of KIM's study.

BERNARD did not believe there was any intent on KIM's part to overexpose the subjects and did not know of any connection KIM may have had to pharmaceutical companies, which could have influenced KIM's study. BERNARD believed the over-exposure may have occurred because it was dosage related and KIM did not follow a policy of notifying the subject's of the changes to the testing protocols. BERNARD opined KIM's work was sloppy, but did not have intent to make the over-exposure dosage error.

BERNARD stated any health problems associated with the subject's normally would have manifested itself within the first six months of exposure to a substance, not four years later.

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF PETER PREUSS

On May 31, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. PETER PREUSS (202/564-3322), Director, National Center for Environmental Research and Quality Assurance (NCERQA), in his office, room number 400G, 808 17th Street, NW, Washington, DC. PREUSS stated he had been during August 2001, and is now, the Human Subject Research and Review Official (HSRRO). PREUSS stated he was the Director of the National Center for Environmental Research during August 2001 when Dr. CHONG KIM's over-exposure of di-2-ethylhexyl sebacate (sebacate) occurred. PREUSS was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

PREUSS stated as the HSRRO, he was delegated by the Administrator the responsibility to oversee human subject research that was funded by EPA or carried out by EPA. PREUSS referred to the 'Common Rule', which he stated received it's name reference because 17 federal agencies signed it in 1991. PREUSS stated the Common Rule laid out the process to ensure human subject research was carried out ethically and appropriately. PREUSS stated his role as the HSRRO was to compliment the Common Rule, and he fulfilled this role once he was informed of KIM's over-exposure of sebacate to subjects. PREUSS stated as Director, NCERQA, every research study involving human subjects by EPA received approval through him.

PREUSS recalled KIM's study had been halted by EPA management at Research Triangle Park, NC at the time and he temporarily stopped all EPA human subject research programs. PREUSS could not recall how long all the human subject study programs were shut down, but stated it was done until then Assistant Administrator for the Office of Research and Development, Dr. PAUL GILMAN, was sure everything that needed to be done was done to evaluate the research methodology.

Investigation Conducted on: May 31, 2005	Conducted at: Washington, DC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 31, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>

PREUSS stated it was his decision, with GILMAN's approval, to contract the Human Subject Review Panel (HSRP) as an external panel to look at KIM's incident as well as procedures to ensure EPA human subject studies were in order. PREUSS stated his goal for the HSRP was to ensure they were independent of the laboratory and EPA.

PREUSS stated there was difficulty in calculating the amount of over-exposure of sebacate the subjects received, but recalled they received a little over 50 times what they consented to receive, in-line with reports stating the over-exposure was 50 - 60 times what the subjects consented to.

At this time, PREUSS stated he assumed Dr. TED MARTONEN, EPA, was the complainant of the allegations to OSC. PREUSS stated he guessed MARTONEN because he had previously pursued the same allegations actively. PREUSS did not know why MARTONEN was pursuing the allegations. PREUSS stated the memorandum sent by GILMAN during July 2004, was written by PREUSS and addressed previous allegations made by MARTONEN. PREUSS stated he knew of MARTONEN, but never worked with him.

PREUSS stated there was no basis for an EPA cover-up of KIM's over-exposure of sebacate to the subjects. PREUSS stated the review was done in an open manner and that EPA management knew what was done. PREUSS stated the HSRP and its members were not secret. PREUSS stated he did not understand the basis of the complaint, based on EPA's openness.

PREUSS stated the HSRP followed-up and made recommendations to EPA. PREUSS stated the review did not find anything wrong or any problems with the subjects of KIM's study. PREUSS stated recommendations by HSRP were accepted by GILMAN and he directed the recommendations be implemented. PREUSS stated the implementation led to new standard operating procedures in the laboratory and more attention to detail than before. PREUSS stated notification to him immediately was one of the recommendations implemented.

PREUSS opined there was no intention by KIM to cause the over-exposure. PREUSS stated it was a "straight forward mistake on his part".

PREUSS stated there was a continual review cycle by EPA to have an outside panel review their processes for human testing. PREUSS recalled the last review was six to twelve months earlier, but believed it was closer to six months ago. PREUSS stated the reviews were to look at the human subject research processes and see what EPA was doing to limit process problems like what occurred with KIM's study.

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF ROGER S. CORTESI

On May 5, 2005, Special Agent (SA) LEONARD O. NEWMARK, Desk Officer, Financial Fraud Directorate, interviewed Dr. ROGER S. CORTESI, Senior Science Advisor, Office of Research and Development (ORD), National Center for Environmental Research, in his office located at 1025 F St. N.W. Rm 3303, Washington, DC. SA NEWMARK presented OIG-OI issued credentials and informed Dr. CORTESI that the purpose of this interview was to identify his involvement in review activities associated with human subject research conducted by Dr. CHONG KIM at EPA's National Health & Environmental Effects Research (NHEERL) Laboratory, Research Triangle Park, North Carolina.

By way of background, Dr. CORTESI stated that he has four general areas of responsibility; lecturing Program Officer classes regarding research misconduct issues, quality assurance within ORD, implementation of human test subject regulations, codified at 40 CFR 26 and referred to as the "Common Rule," and review of proposals for scientific studies that involve human research.

Regarding the specific issues raised by Dr. MARTONEN with respect to Dr. KIM'S research, Dr. CORTESI stated that he has very little "first hand knowledge" of the specifics of this matter as he was primarily reviewing and preparing memoranda and other documents from pre-existing materials. Dr. CORTESI was asked to provide these document, however he stated that he did not maintain them and that they were available at RTP. Dr. CORTESI stated that he had reviewed his records and identified some documents that he prepared that identified his involvement in this matter.

Dr. CORTESI provided the following documentation: memo entitled "GilmanWhitman021001" (Attachment 1); letter dated August 15, 2002 to Dr. MARTONEN, (Attachment 2); and a document titled "Approximate Timeline for Martonen Letter and Replies" (Attachment 3).

Investigation Conducted on: 05/05/05	Conducted at: Washington, DC
Conducted by: SA Leonard O. Newmark	OI File No: 2005-2002
Date Prepared: 05/06/05	Prepared by: LON <i>LD</i>

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INTERVIEW OF ROGER S. CORTESI

Dr. CORTESI was unable to recall when he became involved in this matter, but did state that he has never spoken, or communicated in any way with Dr. MARTONEN. Dr. CORTESI stated that Dr. MARTONEN is extremely bright, but can be irrational. Dr. CORTESI stated that Dr. MARTONEN and his supervisor, Dr. BIRNBAUM do not get along.

Dr. CORTESI stated that ORD procedures require that before any human subject research is undertaken, an "Institutional Review Board" (IRB) composed of staff from the University of North Carolina at Chapel Hill, but no EPA employees, must approve the research. Further, the "Common Rule" requires that evidence, in the form of certifications, be prepared that states that the IRB reviewed and approved the research protocols. Dr. CORTESI stated that additionally, EPA requires a review by a Human Subject Research Review Official. Dr. CORTESI stated that the level of exposure to sebacate in what Dr. KIM proposed, and what was approved by the IRB, was lower than what the human subjects were actually exposed to. Dr. CORTESI stated that any change in the protocols would have had to have been approved by the IRB. Dr. CORTESI opined that he did not think human studies projects were getting adequate oversight.

Dr. CORTESI stated that the issue of exposure to substances greater than that to which human subjects consented had actually been brought to ORD's attention by another incident involving dermal exposure which was conducted by a different researcher under a different experiment. Dr. CORTESI said that although the dermal exposure experiment protocol deviations was the first one brought to ORD's attention, it actually occurred after Dr. KIM's. Dr. CORTESI stated that even in this situation, there was still no risk posed to the human subjects.

Dr. CORTESI said sometime in 2003, after the sebacate dosing issue was brought to ORD's attention, a panel was assembled with four outside experts to study this situation and make recommendations for improvements. Dr. CORTESI stated that he did not recall the names of the experts, but recalled that one was from the University of North Carolina at Chapel Hill, one was from the Department of Health and Human Services, two were from private industry.

Dr. CORTESI said that while it is accurate to say, with respect to Dr. KIM's sebacate experiments, that subjects were exposed to dosages at a higher level than that to which they had consented, the statement by Dr. MARTONEN that this therefore means that the subjects must have been exposed to another more hazardous material, may not be accurate. Dr. CORTESI said that he is not aware of any other substance, aside from sebacate, being used in Dr. KIM's experiments.

Dr. CORTESI stated that there has been no evidence that he has seen that indicates Dr. KIM's experiments created a health risk and no evidence to indicate that the exposure to sebacate in higher amounts than that which the subjects consented to was intentional. Dr. CORTESI did say that there was a nine month time lag in reporting this error to ORD, and that it only came to light after the dermal dosing issue was identified.

INTERVIEW OF ROGER S. CORTESI

Dr. CORTESI stated that he was "confused" by Dr. MARTONEN's assertion that Dr. BIRNBAUM "misdirected" panel deliberations. Dr. CORTESI stated that with respect to the outside expert panel, Dr. BIRNBAUM had no role in the selection of the four individuals, nor in establishing the agenda--though she may have appeared as a witness.

Dr. CORTESI said that in his opinion he did not think there was any cover-up, but that perhaps Dr. KIM made a mistake in not immediately notifying ORD of the sebacate dosing issues.

Dr. CORTESI said that he recalls there were less than ten human subjects in Dr. KIM's experiment and that they were all notified about the dosing error. One individual responded to the notification by stating something to the effect it appeared EPA was more concerned about protecting itself than the test subjects.

Dr. CORTESI stated that "he thinks but does not know" that Dr. MARTONEN, prior to him raising issues regarding Dr. KIM's work, may have allowed people into experiments that he designed that were not specified in the protocol. Because of this, Dr. MARTONEN was not allowed to conduct any further research that involved human subjects.

Attachments

1. GilmanWhitman021001, one page document
2. Letter dated August 15, 2002
3. Approximate Timeline for Martonen Letter and Replies, one page document

GilmanWhitman021001

The purpose of this note is to briefly tell you about two recent incidents at EPA's National Health and Environmental Effects Laboratory [NHEERL] where in research involving human subjects, the subjects were exposed to dosages larger than what was in the protocol and the informed consent, and what our response has been.

The first project was one to find where particles of different sizes were deposited in the lung; the second was a physiology based pharmacokinetic [PBPK] study of bromodichloromethane [BDCM], a disinfection by-product in drinking water. In the first cases the dosing mistake was discovered in the midst of the study and it was stopped. In the second case the dosing mistake was discovered after all human exposures had been completed. In both cases the Institutional Review Board [IRB] was notified and letters sent to subjects telling them what had happened and giving them a 1-800 number to call if they had any questions etc. To date we have gotten six calls concerning the first study and zero concerning the second. The letter also told them that while the doses were higher than detailed in their informed consent, the actual exposures were two orders of magnitude lower than harmful dose levels. We have been unable to find about 25 subjects and we are using a commercial "people locator" to find them.

After the second incident, with BDCM, the NHEERL laboratory director suspended all clinical research, and shortly thereafter EPA's Human Subjects Research Review Official [HSRRO] did the same until he was convinced that the reasons for the problems had been determined and suitable corrective actions were underway.

The HSRRO then assembled an outside panel of four to come to the laboratory for three days, August 19-21, to examine the laboratory's procedures, and to make recommendations. The panel makeup was an academic inhalation toxicologist, a consultant in PBPK experimental work, the chairman of a major academic IRB, and a Federal Government expert in analyzing the reasons for medical errors and recommending fixes. Each panel member wrote a report containing recommendations. These recommendations were accepted by the NHEERL and an corrective action plan prepared.

The HSRRO upon reviewing the corrective action plan found it satisfactory and, on September 23rd, lifted the suspension on human clinical research.

02-08-15

Dear Dr. Martonen:

I am replying to your two letters to Administrator Whitman dated June 28, 2002 and July 1, 2002. I am concerned that you think that EPA is engaging in a "cover-up of unauthorized U.S. EPA human subject experiments."

I have made myself very familiar with the facts and circumstances of the incident you refer to and I conclude that the memorandum [attached], dated May 20, 2002, sent you by Dr. Zenick is correct. The research in question was fully authorized and its dosing error not covered up in any way. Dosing errors are of course serious and we are undergoing reviews, both internal and external, of our policies, procedures and methods so as to reduce the probability of any errors in research using human subjects.

Sincerely,

Paul Gilman, Ph.D.
Assistant Administrator

Approximate Timeline for Martonen Letters and Replies

Jan. 31, 2002	Date on Martonen to the Administrator Letter. Assigned to NHEERL for reply.
May 20, 2002	Date on Zenick's to Martonen reply.
June 28 and July 1, 2002	Dates on two additional letters from Martonen to the Administrator.
August 8, 2002 and ~ Aug. 10 2002	Reply assigned to ORD/NCER, for Gilman's signature. Incomings delivered by Zarba directly to Cortesi for draft reply. Due date originally Aug 16, later extended to Sept 15.
~ Aug. 31, 2002	Draft reply with incomings to Preuss after an informal consultation with Joanne Hogan of OGC.
~ Oct. 23, 2002	Overton stirs things up.
~ Oct. 30, 2002	Incomings and draft reply from Preuss to Cortesi.
Nov. 21, 2002	Cortesi gives Preuss a new draft reply. This reply being drawn after extensive conversations with Zarba and Hogan. We all agreed on what the draft said.
Nov. 26, 2002	Draft emailed to Zenick and he approves it.
Dec. 2, 2002	Preuss meets with Gilman with the draft and the incomings.

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF HAROLD ZENICK

On May 4, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. HAROLD ZENICK, Associate Director for Health, Office of Research and Development (ORD), National Health and Environmental Effects Research Laboratory (NHEERL) at his office, Building B, Room # B120I, at the EPA Facility at Research Triangle Park (RTP), NC. ZENICK was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

ZENICK provided the reporting agent a copy of the NHEERL Human Research Policy and Guidance, dated December 18, 2003 (Attachment 1); Human Research Guidance, Second Edition draft, dated April 2005 (Attachment 2); NHEERL Human Research Policy, dated September 27, 2004 (Attachment 3); memo on the Decision on Suspension of Human Clinical Studies at NHEERL, dated September 23, 2002 (Attachment 4); Human Studies Division's (HSD) Implementation of the Corrective Action Plan dated August 15, 2003 (Attachment 5); and a copy of a Powerpoint Briefing titled "NHEERL Human Research Policy and Guidance" presented by Dr. RICHARD HERMANN, Human Studies Research Group, given to the ORD Executive Council (consisting of the Laboratory and Center Directors, the Deputy Assistant Administrator, and the Acting Assistant Administrator, TIM OPPELT) during April 2005 (Attachment 6).

ZENICK stated NHEERL used interim guidance to regulate studies of Human Subjects, pending the issuance of the Policy and Guidance listed as Attachment 1.

ZENICK stated he was Dr. TED MARTONEN's second line supervisor. Dr. LINDA BIRNBAUM, Director of Experimental Toxicology, was MARTONEN's first line supervisor.

ZENICK recalled the study involving human test subjects receiving di-2-ethylhexyl sebacate (sebacate) was an innocuous particle substance used as a control for an experiment by Dr. CHONG KIM. ZENICK stated sebacate was a non-reactive particle. The study was to test particulate matter of the location aerosol particles were deposited in the lungs and to see how the

Investigation Conducted on: May 4, 2005	Conducted at: Research Triangle Park, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 4, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>

particles were cleared from the lungs. As ZENICK recalled, the study looked at how the particles were cleared from the lungs of people with compromised health and were at risk of not clearing the particles from their lungs. ZENICK stated Dr. BOB DEVLIN was KIM's supervisor and could provide more information. ZENICK believed the sebacate was administered and as the dosage size of the particle was increased, the over-exposure problem occurred because the mass increase of the particles was not calculated. This caused an increase to the overall exposure of sebacate to the test subjects.

ZENICK stated the agency took action against KIM for the over-exposure error and not having signed consent forms, but he could not provide details of that action, due to a legal agreement. ZENICK stated KIM was banned and could no longer conduct human subject studies.

ZENICK stated the several month delay in notifying the subjects of the dosage error was due to resolving the potential legal issues and disciplinary action against KIM. Once those issues were resolved, it took KIM weeks to re-do the calculations to determine the amount of the excess dosage given to the subjects. ZENICK stated at the time, there was not any checks or balances in the system because a second person was not involved in the study. ZENICK stated studies now use a second person who is familiar with the calculations as part of a check and balance system. ZENICK stated the subjects were not notified immediately of any issue of the mis-dosage, because it was determined that there was not a health risk to the subjects. ZENICK stated if there was any issue of human safety to the subjects, he would have explored other options and forced the issue to resolve the re-calculations KIM needed to complete, despite the legal issues which were still unresolved.

ZENICK stated subjects for the experiment were selected after response to campus newspaper advertisements. All the subjects went through a medical screening process before being selected. ZENICK stated the Institutional Review Board (IRB) reviewed KIM's study and cleared the study, including the subjects, to begin the study. ZENICK stated the IRB now does not get protocol changes until the changes are reviewed by HSD, PREUSS, and ZENICK. During KIM's study, approval was only given by HSD before a protocol was forwarded to the IRB.

ZENICK recalled the letters sent to the subjects were from Dr. SEAL, now EPA retired. SEAL was the Human Subject's official and medical ethics officer.

ZENICK stated PREUSS secured the External Peer Review Panel (EPRP). The EPRP reviewed information provided by EPA officials regarding this incident. ZENICK recalled the EPRP took about four months to complete their review. ZENICK stated no EPA employee was on the EPRP, and at most, facilitated the EPRP.

ZENICK stated the NHEERL review completed during August 2003 was the most recent review. ZENICK added NHEERL will follow-up and ask a couple of the EPRP members to do a review before the end of 2005 of HSD with HERMANN, who began work about February 2005. The goal is to see how NHEERL is currently doing.

ZENICK stated DEVLIN could answer the specifics of the amount of sebacate given above what the subjects were told. ZENICK stated there was no intent by EPA or KIM to cover-up the error of over-exposure by KIM. ZENICK recalled KIM was doing the study of the subjects when a technical staff person brought the dosage error, possibly due to instrument calibrations, to KIM's

attention. The error was based on the chamber monitoring not giving the correct dosage of sebacate.

ZENICK believed motivation for MARTONEN to make the allegations may have been because MARTONEN did not believe he had support from EPA management for his programs. ZENICK stated MARTONEN may also believe the allegations were another way to bring attention to MARTONEN's Equal Employment Opportunity Complaint against EPA for not providing support, based on discrimination.

ZENICK stated others who could provide useful information related to this investigation include Dr. NELSON, Dr. MILLER, HERMANN, DEVLIN, and KIM.

Attachments (contained in separate folder)

1. NHEERL Human Research Policy and Guidance, dated December 18, 2003
2. Human Research Guidance, Second Edition draft, dated April 2005
3. NHEERL Human Research Policy, dated September 27, 2004
4. Memo on the Decision on Suspension of Human Clinical Studies at NHEERL, dated September 23, 2002
5. HSD's Implementation of the Corrective Action Plan dated August 15, 2003
6. Copy of a Powerpoint Briefing titled "NHEERL Human Research Policy and Guidance"

December 18, 2003

Human Research Policy and Guidance

**National Health and Environmental Effects
Research Laboratory**

U.S. Environmental Protection Agency

**First Edition
2003**

FOREWORD

In the very rapidly changing world of human research ethics, this NHEERL Human Research Policy and Guidance document compiles the most relevant information to help Principal Investigators, Co-Principal Investigators, Technicians, and Managers understand Federal and EPA regulations for conducting human research, preparing a Protocol Package, and implementing an actual human study. To keep this document reasonably short, only the most commonly occurring types of human studies in NHEERL are included. The names of Human Research Officers have been included in Chapter 1, Section 1.12, as sources of additional information. The reader is very strongly encouraged to contact them for guidance and assistance on a case-by-case basis.

Chapter 1 presents information basic to the conduct of all types of human research likely to occur in NHEERL. Chapter 2 covers studies in which humans are deliberately exposed to environmental pollutants ("clinical studies".) Chapter 3 considers human research in an epidemiological setting. Chapter 4 discusses the ethical handling of specimens and data derived from humans. Chapter 5 details the special requirements for using NHEERL employees as research participants. The Appendices provide information on the Belmont Report, one of the key historical documents in human research ethics; the new HIPAA requirements; and a sample sign-off sheet.

This document will never be "final" in the usual sense of the term. Science has always outpaced ethical and moral concerns in the study of humans. As ethical concerns evolve in an effort to keep up with science, so must this document. Therefore this is only the first edition of a document that will develop and mature with time and with the pace of scientific discovery.

Many people contributed to this document and previous drafts. I would like to acknowledge their valuable insights, additions, and corrections as this document took shape through many iterations.

Elston Seal, Jr., M.D., Director
NHEERL Human Research Protocol Office
December 2003

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CHAPTER 1

GENERAL POLICY AND GUIDELINES FOR THE CONDUCT OF HUMAN RESEARCH

1.1 PURPOSE

As the requirements for human research become more complicated, it has become apparent that there is a need for a standardized set of policies and principles that apply to human research in the National Health and Environmental Effects Research Laboratory (NHEERL) in the Office of Research and Development (ORD) of the U.S. Environmental Protection Agency (EPA). General policies and practices applicable to **all** human research conducted by NHEERL are presented in this chapter. Subsequent chapters provide additional information and requirements for specific types of research: controlled exposures in Chapter 2, epidemiologic studies in Chapter 3, human tissues and in vitro studies in Chapter 4, and use of NHEERL employees as research participants in Chapter 5.

For the purpose of this document, human research is defined as research that directly obtains information (**including information from questionnaires and interviews**) and measurements from humans and their environments, analyzes existing data sets that contain human data and/or studies biological tissue and fluid specimens obtained from humans. Human research at NHEERL includes, but is not limited to, controlled-exposure or "clinical" studies, epidemiologic studies, questionnaires and surveys, in vitro studies of biologic or environmental samples, and studies on data previously obtained from human participants.

1.2 APPLICABILITY, EXEMPTIONS, AND EXEMPTIONS

Any NHEERL Division conducting human research must follow this guidance document, which outlines the requirements and expectations for the ethical conduct of human research at the Laboratory-wide level. To assist researchers, technicians, and managers, each Director of an NHEERL Division conducting human research will appoint a Human Research Officer. This Officer will be the key Division resource for the day-to-day compliance with existing Federal regulations and with the NHEERL Policy and Guidance for Human Research (this document).

Any type of NHEERL research involving human participants in any way must adhere to EPA Order 1000.17, Change A1, 1999, (http://intranet.epa.gov/rmpolicy/ads/orders/1000_17a.pdf), which describes the Agency's implementation of the Federal Policy for the Protection of Human Subjects, also called the "Common Rule," cited in 40 CFR 26. NHEERL research is defined as any activity that is conducted by an NHEERL employee or by an extramural investigator involving an

NHEERL employee (other than as a research subject), and/or using NHEERL resources, regardless of the funding source. The proposed research must then be reviewed and approved by an Institutional Review Board (IRB), an autonomous body required by the Common Rule, which must review and approve human research protocols before they can be implemented. All IRBs are overseen by the Office for Human Research Protections in the Department of Health and Human Services.

1.2.1 Exceptions

Some research activities involving previously collected human data may be an **exception** to the Common Rule because they are **not considered to be human research** for purposes of application of the Common Rule. Examples of such studies include the following.

- Use of publicly available data sets with all personal identifiers removed (that is, there is no means of ever identifying the individual participants.) Some common examples include data sets such as vital statistics and the National Health and Nutrition Examination Survey (NHANES).
- Use of tissues from cadavers. (See also Chapter 4.)
- Use of commercially available biologic specimens and data.
- In some cases, use of stored biologic specimens that have no personal identifiers retained with the sample.

Because it is not always clear whether a particular activity constitutes human research, consultations with the appropriate IRB and the Director of the NHEERL Human Research Protocol Office may be required. Although excepted studies do not require a formal review by an IRB, they do require a brief EPA review. In a memorandum to the Director of the NHEERL Human Research Protocol Office, the Division Director must summarize the study and justify why it is an exception to the Common Rule. The Director of the NHEERL Human Research Protocol Office must concur before the study may proceed.

1.2.2 Exemptions

Certain human research activities are **exempt** from some of the requirements of the Common Rule for ongoing human research review. An example is a study of medical records in which personal identifiers were initially available to the investigator, but which were later stripped from the data. Exempt activities are defined in the Common Rule [40CFR 26.101(b)]. For a study to be exempt, an IRB must first grant an exemption. Then EPA must also review and approve the study as described in Section 1.10, Step 6.

1.2.3 Possible Exemptions

Exposure releases, disease outbreaks, Homeland Security issues, and other events that require a rapid response **may be exempt** from the Common Rule. Researchers should not make the determination of exemption by themselves. Before beginning such studies, the Principal Investigator (PI) must obtain approval to proceed from the Division Director, the Director of the NHEERL Human Research Protocol Office, and the Associate Director for Health or Ecology, as appropriate. **Whenever possible, a rapid review and approval should be obtained from the IRB.** Studies in these categories must otherwise conform to the provisions of the Common Rule.

1.2.4 NHEERL Requirements

Other NHEERL requirements for the conduct of human research, in addition to those required by the Common Rule and by the Agency implementation of the Common Rule described in EPA Order 1000.17, Change A1, 1999, are specified in this document.

1.3 JUSTIFICATION

The EPA mission is to protect human health and safeguard the natural environment. Human research data is vital to achieving the following goals.

- Protection of public health by providing direct insight into the nature and magnitude of risks to human populations from exposure to environmental pollutants.
- Compliance with certain laws and regulations, such as the Clean Air Act and the Safe Drinking Water Act, which specifically require the Agency to conduct research on the effects of pollutants on human health.
- Identification and amelioration of effects on especially sensitive populations, which is a requirement of legislation such as the Clean Air Act, the Safe Drinking Water Act, and the Food Quality Protection Act.
- Assessment of the genetic, life-stage, or life-style factors contributing to individual variation among humans and potentially to increased risks.
- Greater certainty as to which pollutants or components of pollutants are responsible for affecting human health and the mechanisms by which they exert their actions.
- Better targeting of decisions and actions to increase the effectiveness of prevention and abatement programs.

- The most judicious expenditure of finite financial resources.
- Direct evaluation of the success of environmental decision making and practices as reflected in actual public health impact.
- Validation of animal and in vitro methods and models, thus increasing EPA's confidence in other approaches for which the Agency must often place primary reliance. For example, the uncertainty in extrapolating from animal data to humans can be markedly reduced.

1.4 HISTORY

The conduct of human research carries special responsibilities with regard to ethical, medical, and scientific issues. Society, while generally in favor of research on humans, has imposed special requirements on investigators because of concern about mistreatment of human research participants based, in part, on the historical legacy of improper human studies. The following sections summarize key documents tracing the profound changes in human research ethics that took place from immediately after World War II to the present.

1.4.1 Nuremberg Code (1947)

The Nuremberg Code was a direct result of post-World War II war crimes trials of Nazi physicians who committed atrocities on prisoners of war under the guise of medical research. The first principle of the Code is: "The voluntary consent of the human research subject is absolutely essential."

1.4.2 Declaration of Helsinki (Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly Tokyo, Japan, October 1975; 35th World Medical Assembly Venice, Italy, October 1983; and the 41st World Medical Assembly Hong Kong, September 1989)

The most universally accepted human research document. It has been amended numerous times to keep up with the changing research world. In the case of Agency human research conducted in foreign nations, the Declaration of Helsinki may be the strongest assurance that investigators will adhere to an accepted international norm to protect human participants.

1.4.3 Belmont Report (1979)

The cornerstone of U.S. human research ethics documents. The report was completed by a group that met at the Belmont Conference Center of the Smithsonian Institution. It embodies three principles, namely, respect for persons, beneficence, and justice. A more complete description is provided in Appendix A.

1.4.4 “Common Rule” (Federal Policy for the Protection of Human Subjects) [codified by EPA, 40 CFR 26] (1991)

The Common Rule was enacted to bring uniformity and cohesion to a patchwork of existing Federal human research protections. Originally, it was ratified by 16 (now 17) Federal Agencies and Departments, hence the name “Common Rule.” It embodies and expands on the principles of the Belmont Report. The Common Rule establishes **minimum** standards for the conduct of human research funded by the Federal government. **Federal Agencies and Departments can require stricter standards for human research, but cannot weaken the Common Rule requirements.** Common Rule principles, however, have become the de facto standard for much of the human research conducted in the United States, including human research not federally funded.

The Common Rule consists of four parts. Subpart A covers requirements for all human research. Subparts B-D provide additional protections for classes of individuals considered especially vulnerable. Subpart B covers research involving pregnant women, fetuses, and human in vitro fertilization; Subpart C, research on prisoners; and Subpart D, research on children, a topic of increasing concern to the Agency. Section 26.101(b) lists exceptions to the Common Rule in which full reviews of human research studies are not necessary. Any exceptions relevant to NHEERL research are discussed in the following chapters.

1.4.5 EPA Order 1000.17, Change A1 (1999)

This is the EPA implementation of the Common Rule. Everyone in the Agency involved in human research or supervising those involved in human research must be familiar with this Order. See http://www.epa.gov/oamrtpnc/forms/1000_17a.pdf for additional information.

1.4.6 HIPAA (Health Insurance Portability and Accountability Act) (2003)

HIPAA, which became effective in April 2003, includes both the portability of employees' health insurance as employees change jobs (which does not affect human participants research at NHEERL) and the accountability for individual Protected Health Information (PHI) (which does).

HIPAA recognizes three “covered entities”—health care providers, health care information clearinghouses, and health care payers—that must have authorizations from individual patients or research participants before their PHI can be shared and used in research. Because NHEERL is not a covered entity, it ordinarily does not have to comply with HIPAA. However, if human studies are conducted jointly by NHEERL scientists and any type of covered entity, such as the School of Medicine of the University of North Carolina at Chapel Hill, HIPAA authorization is mandatory from each of the study participants.

Other situations that do not require prior HIPAA authorization from study participants include studies on existing data bases, studies conducted in foreign countries, and studies on deceased individuals.

The Director of the NHEERL Human Research Protocol Office has an approved template for preparing a HIPAA authorization form for research participants to review and approve during the informed consent process. A copy of the HIPAA template is found in Appendix B. Consult the Director for additional information on HIPAA requirements.

1.5 TRAINING

The Director of the NHEERL Human Research Protocol Office has oversight responsibility for all training related to the protection of human research participants. All NHEERL researchers administering tests, collecting data, or handling confidential information from participants must have EPA-approved human research training and must update such training annually. They must also provide evidence of satisfactory completion of such training to their Division Human Research Officer. Every January, the Division Human Research Officers will give the NHEERL Human Research Protocol Office an updated list of all currently certified researchers. Similar information is required throughout the year whenever a new researcher is added to a human studies project. This NHEERL-required training is in addition to any training required by the applicable IRB.

There are many ways to fulfill NHEERL training requirements. The NHEERL Human Research Protocol Office will organize a series of presentations on ethics training, to be conducted by experts both inside and outside NHEERL. Initial topics will include an introduction to this guidance document and detailed discussions on how to avoid common mistakes found in protocols and informed consent forms. Divisions are urged to suggest topics that would be most helpful to them. Divisions are also encouraged to develop their own training programs to supplement NHEERL-wide activities.

Researchers may attend in-house "town hall meetings" on ethics; seminars presented by IRB representatives; and national meetings, such as those sponsored by Public Responsibility in Medicine and Research (PRIM&R) and the Applied Research Ethics National Association (ARENA). Listed below are the URLs for several Web-based courses in human research ethics and their sponsoring organizations.

- "Human Participants Protections Education for Research Teams",
National Institutes of Health
<http://ohsr.od.nih.gov/cbt>
- "Education in the Responsible Conduct of Research," University of
Minnesota
<http://www.research.umn.edu/ethics>

- “Research Ethics,” University of Nebraska Medical Center
<http://unmc.edu/ethics>
- “Scientific Integrity,” Virginia Commonwealth University
<http://www.vcu.edu/courses/rcr>

The training listed above cannot take the place of NHEERL-sponsored training on quality assurance/quality control (QA/QC) or laboratory safety. These topics, too, are critical for conducting human studies research.

1.6 INFORMED CONSENT PROCESS

Informed consent is an extremely important process used to ensure that competent individuals freely choose whether to participate in research activities and that they fully understand any risks and potential benefits of participation.

A Web site of the Council of International Organizations of Medical Science (CIOMS), in collaboration with the World Health Organization, (http://www.cioms.ch/frame_guidelines_nov_2002.htm) provides additional background information on the features of informed consent, including ensuring that prospective participants understand the specific research procedures; that the process encourages and responds to their questions; and that the investigators allow sufficient time for them to decide whether to give their consent.

Section 1.2 listed certain types of research that are exempt from the Common Rule and therefore do not require informed consent. Other circumstances may require an informed consent process, but do not require an informed consent form. Some examples are as follows.

- Data collection activities and research that can be anonymous. 45 CFR 46.117 provides for a waiver of signed consent when the retention of a signed consent form would be the only information that links the participant to the study.
- Telephone interviews, Web-based data collections, and other “paperless” research. In many cases, the IRB will not require a consent form. The IRB may require that the investigator document in some fashion that the consent process has taken place.

Except as noted above, all studies involving the collection of human data are required to document consent from participants using a form that was approved through the Agency’s review process, including approval from an IRB. Examples of human data include, but are not limited to, questionnaire data, biologic specimens, other types of health indicators (blood

pressure, height, weight, physical fitness tests, lung function tests, etc.), personal environment collection (house dust, personal wipes, home water samples, etc.), and data extracted from charts. Participants may have to re-consent for a new research activity if the previously collected data will be used in a manner not formally disclosed in the original consent form.

1.7 PROTOCOL PACKAGE OVERVIEW

A Protocol Package describes the proposed study in great detail. The Package consists of many parts: the protocol itself, informed consent form, questionnaires, advertising for participants, Fact Sheet, Study Justification Document, and other components, if necessary. The following sections describe each of these parts in detail.

The Package serves several key functions for the Agency. It justifies why the research must be conducted in humans, rather than in animals or tissues; how the proposed procedures for data and sample collection and analysis will achieve the desired research results and Agency goals; and how the confidentiality and well-being of participants will be protected.

For human research projects, the Principal Investigator (PI) is responsible for preparing the Package, which must be reviewed and approved by both the IRB and EPA before the study can begin. Review and clearance procedures are described in detail in Section 1.10.

Preparation and approval of the protocol, informed consent form, and any other associated documents is a three-stage process. The first stage is review and approval at the Branch level and by the Division Human Research Officer. Then the IRB must approve the protocol, informed consent form, advertising for participants, and any other components it requires. Finally, there is additional EPA management review and approval at the Division level and above. EPA must also approve all of the items approved by the IRB, and, in addition, requires an approved Fact Sheet and Study Justification Document, which are unique to EPA. **Thus, the Protocol Package must be prepared with both the IRB and the EPA requirements clearly in mind.**

1.8 IRB-REQUIRED DOCUMENTS

Documents submitted to the IRB include the protocol, informed consent form, blank copies of questionnaires, copies of advertising to be used to recruit participants, and any other items requested by the IRB. **All of these items must first be approved by EPA before the PI can submit them to the IRB.** (The approval process is described in detail in Section 1.10.1.)

1.8.1 Protocol

A protocol describes the “who, what, where, when, why, and how” of a study. The “who”

describes the study population and the researchers conducting the study; "what," the research to be done; "where," the location of the study; "when," the time frame; "why," the need for the research; and "how," a very detailed description of exactly how the study will be conducted.

Listed in the protocol by name and highest degree are the Principal Investigators (PIs), Co-Investigators (Co-Is), and all other staff members interacting with study participants or handling data linked to personal identifiers of the participants. The nurses, medical staff, and employees of the recruitment contractor, however, need not be listed unless they are PIs or Co-Is.

In addition, the protocol is the springboard to the informed consent form described in Section 1.8.2, because anything found in the informed consent form must have been justified first in the protocol.

Protecting participants' privacy and confidentiality are a primary concern in all protocols. All records maintained on individuals by a Federal Agency must comply with 5 U.S.C. Section 552a of the Privacy Act of 1974. (See <http://www.usdoj.gov/foia/privstat.htm>). In that Act, the term "maintain" includes maintain, collect, use, or disseminate. Privacy concerns are particularly relevant in the collection of human biologic specimens and health indicators.

1.8.1.1 Human Biologic Specimens--

If identifiers are used in the labeling of specimens, the protocol describes how the confidentiality of the participant will be protected. For example, assume that each participant is issued a study identification number (ID). Then the list of IDs, along with the associated participant name, should be kept in a locked location under the control of the PI. All analyses should be conducted using the ID number, not the name of the participant. Only individuals with a need to know to perform their duties should have access to such confidential information, and they should be required to keep such information private.

Collection techniques for biologic specimens must also ensure the protection of the participant so that there is a very high margin of safety and low risk of harm from the collection procedure. A statement regarding the potential harms and prevention of potential harms must be included in the study protocol. Examples of statements for common procedures are available from the NHEERL Human Research Protocol Office.

1.8.1.2 Other Health Indicators--

Measures for protecting the confidentiality of the participant's health indicator data must be included in the protocol. Techniques used to collect health indicator data (blood pressure, height, weight, physical fitness tests, chart reviews, etc.) must have a very high margin of

safety and low risk of harm to the participant from the collection procedure. Statements regarding the potential harms and prevention of potential harms must be included in the protocol. The NHEERL Human Research Protocol Office can provide examples of statements for common procedures.

1.8.2 Informed Consent Form

The basic elements of an informed consent form, taken from the Common Rule, are summarized below. More detailed descriptions are usually found in application packages from the IRB. Informed consent forms should be constructed to comply with instructions provided by the applicable IRB. Informed consent topics are also discussed, as applicable, throughout the five chapters in this guidance document.

1.8.2.1 Basic Elements—

- A statement that the study involves research and an explanation of the purpose.
- Duration of the participant's involvement in the study and an explanation of the procedures to be followed, including experimental procedures.
- A description of any reasonably foreseeable risks or discomforts.
- List of benefits accruing to the participant or to others.
- Description of any alternative procedures or courses of treatment for clinical patients, if applicable.
- A statement describing how confidentiality of the participant's personal information and study results will be maintained.
- Compensation and/or treatment, if any, for injury.
- Whom to contact at NHEERL if a participant believes his or her rights have been breached or if an injury has occurred. NHEERL contacts must be individuals that have no direct interest in the study, such as the Division Human Research Officer and the Director of the NHEERL Human Research Protocol Office. Names and telephone numbers of these officials must be included in the informed consent form. If appropriate, a toll-free number should also be included.
- Whom to contact in the IRB if a participant believes that his or her rights have been breached or that an injury has occurred. The name and telephone

number of the Chairman of the IRB must be included in the informed consent form.

- A statement that participation is voluntary. Refusal to participate will involve no penalty or loss of benefits for efforts already completed.

1.8.2.2 Risks–

The informed consent form should clearly disclose what study participation entails, including the risks and harms that may be encountered during the course of the study. The Federal Tort Claims Act (1946, as amended) should be cited in the consent form as a mechanism for the recovery of damages as a result of injury or illness caused by participation in NHEERL human research studies. The suggested language covering Federal employees is as follows.

“In the event of personal injury resulting directly from the research procedures, financial compensation cannot be provided under the Federal Employee Compensation Act. In the event that physical injury is proximally caused by the negligence of a federal employee, the federal government would be liable in accord with the Federal Tort Claims Act (28 USC 2671-2680.)”

This Federal disclaimer is mandatory whenever an NHEERL employee is conducting human research. NHEERL is not covered by the disclaimer of a non-Federal organization such as the School of Medicine of the University of North Carolina at Chapel Hill, a frequent research partner. Whenever NHEERL is cooperating with non-Federal organizations in the research, these organizations must also include their own disclaimers in the section on Risks.

1.8.2.3 Incentives–

The use of incentives, such as financial compensation or non-monetary items, must be clearly disclosed within the informed consent form. Incentives used to enhance participation in studies should not be such that participation is manipulated or coerced. The NHEERL Human Research Protocol Office can provide examples of typical compensations for various procedures.

1.8.2.4 Voluntary Participation–

The informed consent form needs to specify that participation within the study is voluntary and that participants can withdraw from the study at any time. Particular attention needs to be paid to participants who are also clinical patients of the investigators. The consent form must clearly state that refusal to participate in or withdrawal from the study will not affect future treatment from the physician-investigators.

1.8.2.5 Follow-up with Participants—

The types of follow-up must be defined clearly so that the participants know what is required of them and what information will be provided to them.

Determining Follow-up with Participants

The informed consent form should state whether participants will be contacted for additional follow-up for research purposes. Research follow-up is not allowed in the following cases.

The informed consent form states that no follow-up or further contact will be made with the participant.

The participant withdrew from the study.

The participant refuses follow-up during the informed consent process.

Reporting Personal Results to Individual Participants

Each protocol for studies that collect and analyze biologic specimens, health indicators, or personal environment data must provide the rationale for whether individual participants should receive their personal results. An important aspect to consider is the release of study results to a third party, such as the participant's clinician.

All results released to the participant must have an explanation of the test, what are considered reference values, and the possible health indications, if any are known, of the participant's results.

The research protocol and consent form must clearly state whether results will be released to the participant; whether results will have a potential to be released to a third party, with a plan to obtain consent for this release; and whether results will be released to a third party upon request of the participant. The options for sharing results can be categorized as follows.

Results always shared. For screening results that have a clinical significance, such as cholesterol results and blood pressure measurements, and that may have a benefit for the overall health and welfare of the participant, these types of results should be made available to participants and/or their clinical providers, if the participant so chooses. If the researcher conducts tests that show a potential health hazard that may or may not have been detected by the participant or his or her clinician, then the research protocol needs to clearly state how the researcher will address such outcomes.

If such tests will not be available to the participant in a manner timely enough to have an impact clinically for the participant, then a statement to that effect should be noted in the consent form.

Some results shared. If the protocol permits sharing of some results, a suggested option in the informed consent form is to have a choice for participants of whether they would like to receive their personal results. All participants may not want to receive their personal results or may obtain their results only on request. An exception to this choice would be for results that may have a health implication that should be treated by a clinician. These results will be provided to the clinician at the request of the participant.

No results shared. If the protocol provides justification for not sharing results with the participants, a statement to that effect must also be included in the informed consent form. For clinically relevant results, however, justification must be made within the study protocol and consent form as to why researchers will not make the option to obtain these results available to participants.

Reporting Final Study Results to Participants

The protocol must also provide the rationale as to whether an overall report of the study findings, along with an explanation of the findings, will be sent to the study participants.

1.8.3 Questionnaires

Blank copies of all questionnaires must be included in the Protocol Package. **As a requirement of the Paperwork Reduction Act of 1995, review and approval of any surveys to be administered to TEN or more participants must first be obtained from the Office of Management and Budget (OMB).**

Exceptions: Questionnaires and interviews used to interpret results from personal and family medical histories, physical examinations, and other medical tests are exempt from the above requirements of the Paperwork Reduction Act, as are questionnaires from a study in which biologic samples are collected or routine clinical measurements are performed. (See 5 CFR 1320.3, Section h, Item 5.) PIs must not make the determination of exemption themselves but should contact the Director of the Human Research Protocol Office for assistance.

Each study utilizing questionnaire data must provide information on storage of records, including storage of identifying information, such as stating that information and questionnaires will be stored in separate locked locations.

1.8.4 Advertising

Copies of proposed advertising to recruit participants must be included. The advertising must not be coercive or place undue emphasis on remuneration. If there is a recruitment contractor, the PI should consult with the contractor prior to developing the advertising.

1.8.5 Other Components

Each IRB may have its own additional requests or requirements, which must also be honored. For instance, the IRB governing human studies carried out in the School of Medicine of the University of North Carolina at Chapel Hill is also used by the NHEERL Human Studies Division (HSD) to review many of its research projects. That IRB requires evidence that every effort will be made to recruit women and minorities for a study, consistent with the requirements of the research. That IRB has also asked to see comments from external scientific reviewers of controlled-exposure studies to aid in assessing HSD protocols and informed consent forms.

1.9 EPA-REQUIRED DOCUMENTS AND WRITTEN REVIEWS

EPA requires several documents and written reviews in addition to those required by the IRB. Prior to IRB submission, EPA may require written reviews by a physician, statistician, external scientific peer reviewers, and others as necessary.

Following IRB approval, EPA must review and approve all documents submitted to the IRB and the IRB approval notice. Additional documentation is also required: a Study Justification Document describing the importance of the research to an EPA Associate Director for Health or Ecology, as appropriate; and a Fact Sheet explaining the research in more general terms for a broader, non-technical audience.

1.9.1 Initial EPA Reviews

The Branch Chief will determine whether a protocol requires review by a physician, a statistician, and other experts. These written reviews will be attached to the package prior to Branch approval, but are not required for submission to the IRB for review.

1.9.2 Scientific Peer Reviews

Prior to submitting a protocol to the IRB, the PI is responsible for obtaining any EPA-required reviews by technical experts outside the PI's Division. The primary objectives of the reviews are to obtain comments on scientific merit, the value added by conducting human research rather than animal or in vitro research, and whether issues of ethics, participant safety, and participant risks are adequately addressed.

The number of required reviews depends first on whether the participants are deliberately

exposed to any chemical, physical, or biological agent and then on the size and purpose of the study.

Any study, whether pilot or full-scale, that deliberately exposes participants to such agents requires at least one scientific review. Full-scale studies of controlled-exposure of participants to agents that are known pollutants require two external reviews. Full-scale epidemiologic studies with no deliberate exposure of subjects to agents require one external review.

Pilot studies not involving controlled exposure are treated on a case-by-case basis regarding external reviews requirements. Based on what specifically is being piloted, the PI, Branch Chief, and Division Human Research Officer jointly decide on the need for external reviews. If consensus cannot be reached, the Director of the NHEERL Human Research Protocol Office will make the final decision.

The IRB has requested that for controlled-exposure studies these scientific reviews be attached to the package for IRB review.

1.9.3 Study Justification Document

Every protocol must be accompanied by a Study Justification Document, which the PI prepares specifically for the Associate Director for Health or Ecology, as appropriate, with the following issues addressed explicitly.

- Relevance of the research to the Agency's mission.
- Clear justification of the value added by human studies, emphasizing why existing animal or tissue studies are insufficient for this particular research.
- Value added to society in the form of anticipated public health benefit.
- Value added to decision-making in the form of scientific merit.
- Participant safety of paramount consideration.

Risks to participants are minimized by careful planning and design.

Risk assessment calculations, if any, are summarized from the protocol.

The study is justified on the basis of ethical considerations such as risk to the participant against the anticipated benefits to the participant or to society. Because there is little or no benefit to the individual participants in most human studies, it is critical to balance the

potential risks to participants against the importance of the study. Many human exposure studies entail negligible risk. But as the risk to the participant increases, the potential benefit of the study to EPA and to society must be more compelling. In all cases, the risk to the research participants must be minimized and fully disclosed.

- Certification that all NHEERL researchers who administer tests, collect data from participants, handle confidential information, or are otherwise listed on the protocol are compliant with the latest NHEERL requirements for investigator education.
- Detailed communication strategy for reporting study planning and results to interested parties such as EPA Regions and the communities that participated in the study, if appropriate. (The strategy for communicating results to the participants is described in the informed consent form.) The anticipated time-frame for distribution of results must be included.
- Copies of reviewers' comments are also attached. (See Section 1.10.1, Step 2.)

1.9.4 Fact Sheet

A Fact Sheet provides a brief summary of any high-visibility issue, project, or activity to the Assistant Administrator of the Office of Research and Development (ORD) and, when warranted, to the Administrator. Most NHEERL projects involving human research will require a Fact Sheet. The Branch Chief, in consultation with the Division Director, will determine whether a Fact Sheet is required.

Fact Sheets, although for internal EPA use, are written in a **non-technical, jargon-free** style because information from Fact Sheets is also used by the EPA Office of Public Affairs and by Regional and Program Offices to disseminate information about Agency research projects to interested parties, including the general public.

Fact Sheets may be required both at the beginning of a research project and upon peer-reviewed publication of the results. They must be **no more than one page** in length and written in a standard format shown below. A bulleted list is no longer required. Researchers should develop the first Fact Sheet early in the protocol-preparation process and submit it to the NHEERL Public Affairs Officer who will assist them, if necessary, in writing for a non-technical audience. After approval by the Division Director, the NHEERL Public Affairs Officer, and the Associate Director for Health or Ecology, the Fact Sheet becomes part of the Protocol Package for EPA review. The NHEERL Public Affairs Officer sends copies to ORD senior management, as appropriate.

A Fact Sheet at the beginning of a study must include the following five categories.

- Impact Statement:** Explain why is this research is important to the Agency, emphasizing the benefits to be gained by the Agency.
- Background:** Explain why this research is being conducted.
- Study Description:** Provide a brief, non-technical description.
- Timeline:** Include projected starting and closing dates, and current status of IRB and EPA reviews.
- Contact:** Give name and telephone number of contact person.

At the completion of a major phase or of the study itself, the Fact Sheet should be updated with the following additions:

- Results:** Describe the findings, including strengths and limitations.
- Conclusions:** Explain both technical and policy implications.
- Manuscript:** Include complete online and print citations. A single Fact Sheet can cover multiple publications if they occur in the same general time frame.

The NHEERL Human Research Protocol Office will assist investigators in preparing Fact Sheets and maintains a complete file of NHEERL Fact Sheets for reference and review.

1.9.5 Intramural Research Protocol

All key activities described in the protocol, including data handling and sample handling to collect, transport, store, analyze, and dispose of human biologic specimens, are subject to strict QA/QC procedures, which are described in an Intramural Research Protocol (IRP). The IRP, although not formally a part of the Protocol Package, is prepared in parallel with it. The Division QA Officer reviews and approves the IRP prior to review by the Division Director.

1.10 PROTOCOL CLEARANCE PROCEDURES

Protocol clearance procedures vary somewhat, depending on whether the research is performed primarily within NHEERL or with organizations outside NHEERL. Clearance occurs in multiple stages. **Throughout, the PI is the focal point of the clearance procedures.** For studies with a non-NHEERL PI, an NHEERL Co-I will assume responsibility for clearance procedures if the PI does not.

1.10.1 Research Primarily Within NHEERL

The entire NHEERL Human Research Protocol Package (hereafter called the Package) is reviewed in stages by the IRB and EPA. All reviews and approvals in the following procedure are obtained in writing, using a sign-off sheet similar to that shown in Appendix C.

- **Step 1. Protocol Preparation.** Following the instructions of the applicable IRB, the PI and co-investigators prepare drafts of the protocol and the informed consent form. The PI presents the proposed study to a meeting of all interested parties, such as other scientists, medical personnel, biostatisticians, Division Human Research Officer, and the Division QA Officer, for comment. The PI incorporates any necessary changes into the protocol and the informed consent form.
- **Step 2. Initial Reviews.** The PI must obtain any medical, statistical, and other written reviews required by the Branch Chief, and, based on these inputs, must either revise the protocol or provide written justification for not doing so.
- **Step 3. Peer Reviews.** In most cases, the protocol and informed consent form will also require written scientific review from experts external to the PI's Division, who are selected by the PI's first-line supervisor. (See Section 1.9.2 for details.) The PI must revise the protocol and informed consent form as suggested by the reviewer or provide written justification for not incorporating the reviewer's suggestions.
- **Step 4. Branch Chief and Division Review.** The Branch Chief and Division Human Research Officer must review and approve the protocol, informed consent form, and any other items **before** the PI sends these items to the IRB. A copy of the protocol and informed consent form must also be given to the Division QA Officer for comment prior to submission to the IRB. (The Division QA Officer gives final review and approval in Step 6, after IRB approval.)
- **Step 5. IRB Approval.** Only after the above steps are completed can the PI send the protocol, informed consent forms, peer reviews, and any other information required by the IRB to the IRB for review and approval. The PI must notify the Branch Chief and Division Human Research Officer if significant alterations to the initially submitted protocol were required by the IRB as a condition of approval. (Preparation of the Intramural Research Protocol describing QA/QC procedures for review and approval by the Division QA Officer can be done concurrently with the IRB review process.)
- **Step 6. EPA Administrative Approval.** After IRB approval, the PI adds the Study Justification Document, the Fact Sheet, and the letter of approval

from the IRB, and sends two copies of the complete Protocol Package for approval first to the Division QA Officer and then to the Division Director. Upon approval, the Division Director forwards both copies of the Package to the Director of the NHEERL Human Research Protocol Office, who, after approval, sends one copy of the complete Package to the Associate Director for Health or Ecology and keeps a second copy for the official Agency files. Upon approval, the Associate Director forwards the Package to the Agency Human Subjects Research Review Official (Agency Review Official) for final Agency review and approval.

- **Step 7. Study Commencement.** Actual recruitment and study of human participants can begin only after the Agency Review Official sends a memorandum of approval to the PI and the Director of the NHEERL Human Research Protocol Office.
- **Step 8. Record Keeping.** The PI sends copies of the approval memorandum from the Agency Review Official to the Branch Chief, Division Director, and Division Human Research Officer. Because the Protocol Office maintains the official Laboratory file on all NHEERL human research projects, the PI must also ensure that the Office has a complete file, including updates to the entire Protocol Package and copies of all memoranda of approvals.

1.10.2 Research Involving External Organizations

1.10.2.1 Collaborative Research Primarily Outside NHEERL—

Whenever possible, to protect confidentiality in studies not planned by NHEERL, data should be transferred to NHEERL with no personal identifiers. Such anonymous data may be exempted from the provisions of the Common Rule. Consultation with the Director of the NHEERL Human Research Protocol Office is needed to determine whether the study also will need approval from the IRB committee used by the individual Division.

When working with colleagues outside NHEERL, an NHEERL investigator must carefully distinguish between being a collaborator (a major contributor to the study) or a consultant (a minor contributor) because the approval requirements are different.

A collaborator has a substantial involvement as a co-PI, co-investigator, or in activities such as interpreting data and drawing conclusions with the expectation of co-authorship of publications. In these cases, full review and approval of the study by the Director of the Human Research Protocol Office, the Associate Laboratory Director, and the Agency Human Subjects Research Review Official must be done prior to investigator participation in actual recruitment and study of human research participants.

A consultant, however, who provides advice or renders a service without the expectation of co-authorship, does not require any prior approvals before performing the activities.

- With Other EPA Laboratories and Centers in ORD. If NHEERL researchers are major collaborators (co-PIs, co-investigators, or planned co-authors) with another EPA organization, such as the National Exposure Research Laboratory, all requirements of each EPA organization must be met. Ordinarily, the lead organization will obtain any needed external reviews and IRB approval. If not, the NHEERL collaborators will do so. They will add any other NHEERL-required documents, and send two copies of the package through the NHEERL clearance procedures shown in Section 1.10.1. If NHEERL collaboration is minor as defined above, no such NHEERL reviews are required.
- Outside EPA. NHEERL researchers often collaborate with colleagues from universities, medical schools, and other government agencies who take the lead in designing a study. In cases where the research is conducted primarily in NHEERL facilities, the review and approval process is the same as for an NHEERL-led study (see Section 1.10.1). In other cases, the early stages of EPA review (Section 1.10.1, Steps 1, 2, and 3) may not be required. Instead, the following documentation is required for EPA approval: a cover memorandum summarizing the study and the NHEERL involvement; a copy of the IRB-approved protocol; blank copies of IRB-approved informed consent forms and questionnaires; IRB approval letter; Fact Sheet; and Study Justification Document. Two copies of this documentation is then sent through the Branch Chief and Division Human Research Officer to the Director of the NHEERL Human Research Protocol Office for review and approval. Subsequent reviews and approvals are made by the Associate Director for Health or Ecology and the Agency Human Subjects Research Review Official. The sign-off sheet shown in Appendix C is modified as necessary.

1.10.2.2 Research by Outside Users—

Proposed studies that do not require EPA personnel, EPA funding, or EPA-funded contractor support, but are conducted in NHEERL facilities, have a different approval process from that described in Section 1.10.1. Parties interested in using NHEERL facilities should contact the Office of the appropriate Division Director, which will make the referrals. Because the Agency recognizes and appreciates that outside user requests may contain confidential or proprietary information, it will protect that information accordingly.

For proposed studies involving human research participants to be carried out in EPA facilities without EPA involvement, the outside user must submit an IRB-approved protocol and informed consent form and a copy of the approval from the funding organization to the

Division Director for concurrent review and approval by the Division Director, the Director of the NHEERL Human Research Protocol Office, and the NHEERL Associate Director for Health. All reviews are to be completed within 5 to 10 business days. Written approval from the Division Director is required for the project to proceed.

For proposed studies not involving human research participants, the Division Director will decide on the request on a case-by-case basis.

No work can begin in an NHEERL facility until the entire NHEERL review and approval process is completed.

1.10.2.3 Collaborative Research Outside the United States—

If the proposed research includes activities that will be conducted in a foreign country in whole or in part, approval from the EPA Office of International Activities (OIA) must be obtained. Additional information may be obtained at <http://www.epa.gov/oia/>. All NHEERL research (either initiated or through collaboration) conducted outside the United States must comply with the same standards as set forth in the Common Rule, 40 CFR 26, or with the Declaration of Helsinki.

The EPA PI or Project Officer is responsible for obtaining assurance from foreign investigators that the requirements of the Common Rule for participant protection are at least equivalent to that afforded in the United States. Because some foreign investigators are not familiar with the Common Rule, this assurance can sometimes be accomplished by obtaining written documentation from the foreign investigator's institution stating that it adheres to an internationally recognized document, such as the World Medical Association's Declaration of Helsinki, as amended. The same clearance procedures outlined in Section 1.10.1 must be followed.

1.11 AMENDING AND RENEWING PROTOCOLS

Once a protocol has been through the full clearance procedure in Section 1.10.1 and subsequent amendments to the protocol are needed, the clearance procedures will depend on whether the amendments are minor or major. Investigators are encouraged to seek assistance from the NHEERL Human Research Protocol Office in determining whether proposed amendments are major or minor.

1.11.1 Amendments

- **Major amendments.** Amendments that would change the essential character of a study, such as changes in dosing regimens, performing new medical procedures on participants, or obtaining additional data from them must go through an extensive review process. Before the amendment can be submitted to the IRB, it first must be approved by the PI's Branch Chief, QA

Officer, Division Human Research Officer, and the Director of the NHEERL Human Research Protocol Office.

- **Minor amendments.** Amendments that do not change the basic nature of the study, such as adding another staff member to the protocol, adjusting the number of participants, changing data collection methods, editing survey questions to improve clarity, or modifying the remuneration to participants, are considered minor amendments. Minor amendments will not need to go through the full clearance procedure. Before the PI submits the amendments to the IRB, his or her Branch Chief must approve the changes.

After IRB approval is received, the PI must send copies of the amended protocol and the IRB approval notice to his or her Division Director, Division Human Research Officer, and the Director of the NHEERL Human Research Protocol Office for archiving.

1.11.2 Renewals

Approved protocols must be renewed annually, or more frequently, depending on the requirements of the IRB.

- If the protocol needs no amendments, a copy of the completed IRB renewal application and the IRB-approved extension must be submitted by the PI to his or her Branch Chief. After the IRB approves the extension, a copy of the renewal notice is sent to the Division Director, Division Human Research Officer, and the Director of the NHEERL Human Research Protocol Office for archiving.
- If amendments to the protocol are needed, then the procedures outlined in Section 1.11.1 must be followed.

1.12 HUMAN RESEARCH OFFICIALS

The Director of each Division engaged in human research will appoint a Human Research Officer whose responsibility is to assist investigators in preparing Protocol Packages and in maintaining compliance with Federal and EPA regulations. The Director or Interim Director of the NHEERL Human Research Protocol Office is responsible for coordinating, assisting, and providing specialized training for the Division Human Research Officers.

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Experimental Toxicology Division: Thomas Hughes, M.S.
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Mid-Continent Ecology Division:
Neurotoxicology Division: Robert MacPhail, Ph.D.
Reproductive Toxicology Division: Sally Darney, Ph.D.
Western Ecology Division:

CHAPTER 2

GUIDELINES ON THE CONDUCT OF CONTROLLED-EXPOSURE STUDIES

2.1 PURPOSE

This chapter describes the principles and guidelines governing the conduct of controlled exposures of humans to pollutants (often called “clinical studies.”)

2.2 POLICY

This policy extends the general policies discussed in Chapter 1 into the area of clinical studies, and specifically, to controlled human exposure studies. Therefore, all policies in Chapter 1 are incorporated by reference in Chapter 2.

2.3 DEFINITION

Controlled-exposure studies involve the deliberate exposure of humans to pollutants under carefully controlled conditions. Because participants are being deliberately exposed to pollutants and because the gains from the research are often societal rather than individual, it is imperative that the risks to the participants be minimized to the greatest extent possible.

2.4 VALUE

2.4.1 Health Impacts

Exposure of humans to a given condition or stressor affords the unique opportunity to isolate, describe, and explain any health events associated with such an exposure. This research may permit a better understanding of the specific nature and biological mechanisms that underlie the response seen at low-dose exposures in the real world. Such work may also include gaining insights into how human exposures actually translate into “dose” by showing how the body absorbs, distributes, metabolizes, and eliminates the agent.

The controlled-exposure setting also allows for the control or elimination of the contribution of other factors that might confound interpretation. The insights thus gained can be invaluable in understanding whether a given exposure contributes in any substantive manner to given health risks, and in allowing for more specific and targeted regulatory decisions and risk reduction or risk prevention strategies.

There is substantial precedent for the conduct of controlled exposures of humans to a wide range of conditions or stressors in a laboratory setting. A few examples are as follows.

- Phase 1 Clinical Pharmaceutical Trials. Usually performed on healthy, normal participants to establish a safe dose for further testing. The healthy individuals receive no benefit but may be at risk for adverse events.
- Vaccine Trials. Use control groups, who receive no vaccine and also no individual benefit.
- Dietary Supplementation/Depletion Studies. Observe impacts of dietary changes on human health.
- Additional Types. Manipulate chemical, physiological, physical, and/or psychological variables and assess the impact on function and performance.

2.4.2 Policy Implications

Controlled-exposure studies have been the basis for many of the nation's public health decisions, policies, and practices. In most cases, a common thread is that the individual participant may experience marginal risk to his or her health while receiving little direct benefit. The benefit to society, however, can be substantial.

2.5 SPECIAL CONSIDERATIONS

2.5.1 Additional Safeguards

Controlled human exposure studies will not be initiated unless there are prior data from at least one of the following types of research.

- Toxicity testing in animals.
- Other human exposure research, such as epidemiologic studies or controlled human exposures.
- Study of a very closely related chemical compound.

These data are then used as follows in the current study.

- To help design the study.
- To clarify additional insights and benefits to be gained from the study

- To demonstrate the added value these human data will provide to EPA above that which would be obtained from animal or in vitro toxicological studies.

2.5.2 Pollutant Selection and Administration Criteria

The pollutant in question must be present in the environment of interest or may be introduced into that environment. Exceptions might include the use of well-characterized test substances for dosimetry studies. These compounds are not necessarily found in the environment, but they are related to those that are, and they are safer to use.

Because the research results can be used in the regulatory standard-setting process, the duration and exposure dose should be relevant to real-world exposure scenarios. Most controlled-exposure studies involve a single or a few acute exposures of short duration (usually a few hours.) It may be necessary to extrapolate the dose received during such an exposure to the dose received in a real-world setting during a longer exposure (such as 24 hours.) It may also be desirable in some dose-response studies to expose people to slightly higher concentrations of a pollutant than might normally be encountered in the environment. In these cases, the PI must provide convincing evidence that these higher concentrations will not be harmful to the participant.

Once a pollutant is selected for study, a review of the relevant literature of the proposed pollutant must be undertaken. The review will include topics such as toxicology, epidemiology, and structure-activity relationships, to identify and characterize routes of administration to participants and to develop specific expectations of human responses.

Initial studies of a pollutant must be carried out on the least susceptible participants and must be evaluated to assure that the responses of these least susceptible participants conform to *a priori* expectations.

The potential risk, or lack thereof, to the participant must be addressed. Because there is little or no benefit to the individual in most NHEERL human exposure studies, it is crucial that the potential risks to the participants be balanced against the importance of the study. Many controlled human exposure studies entail negligible risk. As the risk to individuals increases, however, the potential benefit of the study to EPA and to society must be more compelling.

2.5.3 Protocol Preparation

In addition to the steps listed above for the preparation of all NHEERL human studies protocols, the following steps must be undertaken for controlled-exposure studies or for those that involve the collection of biologic specimens or physiologic measurements.

2.5.3.1 Initial Steps--

For studies using on-site contractors for participant recruitment or engineering support, or requiring use of the Medical Station, the PI must obtain input from appropriate Project Officers and the Medical Station staff. In these cases, the study outline must contain sufficient detail so that these personnel can ascertain the roles they are being asked to play.

2.5.3.2 Medical Review--

All human studies that involve controlled exposure to pollutants or collect physiologic measurements or biologic specimens on-site must have a medical review. The purpose of this review is to assure that the protocol conforms to accepted medical practice. Primary components of the review include the risks inherent in the procedures proposed and the appropriateness or special considerations of risks for the proposed participant population. A physician-PI cannot review his or her own study. A physician co-investigator, however, can provide the medical review.

2.5.3.3 Dosage Delivery Assurance--

Most controlled-exposure studies in NHEERL take place in the Human Studies Division where pollutants are prepared and delivered by the on-site engineering support contractor, who follows rigorous QA/QC procedures to ensure accurate and reproducible delivery of pollutants to participants. In some studies, however, the substance must be either prepared or administered by the PI or another team member. In these instances, the PI must develop a suitable research operating procedure (ROP) describing the preparation and administration of the substance. The ROP includes, but is not limited to, preparation and delivery of pollutants and the administration of substances such as experimental medications, chemical compounds, dietary supplements, and diagnostic materials to be used as part of the protocol. In consultation with his or her Branch Chief, the PI will submit the ROP for review by an appropriate outside expert. The PI will incorporate suggested modifications, additions, and deletions into the final ROP. Whenever possible, preparing and dispensing substances should be done by an appropriate facility with experience and expertise in this area, such as the UNC Investigational Drug Pharmacy

Prior to beginning a study, the PI must obtain independent verification of the stability, homogeneity, and concentration of the dosing agents. At regular intervals during the study, the PI must also obtain follow-up analyses to ensure that conditions have not changed since the last analysis. This latter requirement may be waived for substances whose composition, purity, and stability are certified by the supplier, such as FDA-approved substances.

In some studies, such as dosimetry studies involving the inhalation of sebacate particles, the preparation and/or administration of substances is not conducive to the use of either an on-site contractor or facilities such as an Investigational Drug Pharmacy. For these studies, the PI must be able to document during each exposure the amount of material that is

administered to the participant. This procedure must be clearly described in the protocol. If not, the study will not be allowed to begin until the QA Officer and PI's Branch Chief are satisfied with the accuracy and reproducibility of the procedure.

These requirements do not apply to the use of over-the-counter and prescription medications that are listed in the Medical Station's Standing Physician Orders. They also do not restrict the use of medications not part of the study protocol that are prepared, administered, and/or prescribed to study participants for health reasons or clinical procedures performed by licensed medical staff involved in the studies. This policy does apply, however, to study protocols that use drugs, compounds, and supplements in a manner that deviates from their FDA-approved use, such as varying the route, interval, or method of administration, or changing the dosage.

2.5.4 Protocol Implementation Meeting

In addition to the procedures described in Chapter 1, and after final approval by the Agency Human Subjects Research Review Official, the study investigators must convene a meeting of all parties except the participants, such as investigators, nurses, recruiters, engineers, and physicians, to answer questions and review the logistics of the study before any participants are actually studied. A "dry run" covering everything except pollutant exposure is strongly encouraged to test the proposed protocol.

CHAPTER 3

GUIDELINES ON THE CONDUCT OF EPIDEMIOLOGIC STUDIES

3.1 PURPOSE

This chapter describes the principles and guidelines for conducting epidemiologic studies in NHEERL.

3.2 POLICY

These policies extend the general ones discussed in Chapter 1 into the area of epidemiologic studies. Therefore all policies in Chapter 1 are incorporated by reference in Chapter 3.

3.3 DEFINITIONS

“Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems. ‘Study’ includes surveillance, observation, hypothesis testing, analytic research, and experiments. ‘Distribution’ refers to analysis by time, place, and classes of persons affected. ‘Determinants’ are all the physical, biological, social, cultural, and behavioral factors that influence health. ‘Health-related states and events’ include diseases, causes of death, behaviors, reactions to preventive regimens and provision and use of health services.”¹

Epidemiologic studies use many different methods to explore both adverse and protective outcomes associated with exposures and risk factors to humans. They can be categorized into two main areas, observational and experimental.

3.3.1 Observational Studies

At a point in time or over time, observational studies investigate changes and/or relationships between selected characteristics and other factors. Observational studies comprise the majority of epidemiologic studies in NHEERL.

¹Last, John. A Dictionary of Epidemiology, Fourth Edition. NY: International Epidemiological Association, 2001.

3.3.2 Experimental Studies

Experimental studies in epidemiology include clinical trials and field trials. Panel studies, which have both epidemiologic and clinical characteristics, are also covered in this section because they are more like epidemiologic studies, in that deliberate exposure to pollutants is not involved. An example of a panel study would be measuring the concentration of pollutants in the air outside the home of a participant who was also undergoing controlled-exposure studies. In experimental studies, the conditions are under direct control of the investigator. Experimental clinical trials are not covered in this chapter, but in Chapter 2 on controlled-exposure studies.

3.4 SPECIAL CONSIDERATIONS

In addition to the guidance offered in Chapter 1, the following ethical and procedural issues associated with epidemiologic studies must be considered.

3.4.1 Participant Burden

The expected participant burden must be considered and described in the protocol. Participant burden includes not only the time and effort needed to complete the study (transportation to the study site, appointments available only during certain hours, questionnaires to be mailed back, etc.) but also exercise tests, medical examinations (including venipuncture), and even the psychological stresses of participation.

3.4.2 Personal Environment Sample Collection

Protection of the participant's personal property and quality of life is especially important when collecting environmental samples (house dust, personal wipes, water samples, etc.) from a participant's home or work area. Methods used to collect, transport, store, analyze, and disposal of personal environmental samples must always protect the confidentiality of the participant and the participant's personal environment.

3.4.3 Spatial and Geographic Information Systems (GIS) Data

Spatial and GIS data can be very useful in examining patterns of exposures and/or outcomes in a given geographical area. Such data, however, must be carefully used with respect to storage and reporting results.

3.4.3.1 Storage-

In addition to sample- and data-handling procedures found in Chapter 1, under Section 1.8.1; spatial and GIS data require additional precautions in handling. By

definition, spatial and GIS data are considered "identifiers;" thus, whenever these data occur in a database, they must be password-protected if stored on a local or network drive. Spatial and GIS data on discs (CD-ROM, floppy, zip, etc.), tapes, and printouts must be stored in a locked facility, such as a locked filing cabinet or storage room.

3.4.3.2 Reporting Results-

Spatial and GIS data must be reported as aggregate data so that no one individual within the data set can be identified from either spatial results or GIS mapping.

Spatial or GIS mapping must not be used in reporting if data are collected in a sparsely populated area, such as a rural community or a small town, or if there is a rare outcome or exposure with the potential to identify a specific individual.

3.4.4 Community-based Observational Studies

In certain instances, such as collecting drinking water or outdoor air samples, personal environment collection may have implications not only for the individual from whom collection is obtained but also for a community as a whole. In these cases, consideration of community notification and/or participation is necessary. Formation of community advisory boards may also be necessary. The protocol must state whether the community as a whole should be informed of the research before it will be conducted and of the results after the study is completed; how the community will be notified, if necessary; and whether community advisory boards will be formed.

Additional procedures are needed for conducting community-based observational studies. Ethical considerations are required both for the individual participants in the study and for the community as a whole. The following communication procedures need to be considered as part of the planning process and the results of these deliberations must be included in the Study Justification Document.

- As part of the study planning process, a communications plan should be developed to inform local, State, and the appropriate Regional EPA Office of the proposed study. The Fact Sheet developed for the EPA Protocol Package can be used as part of this process.
- If requested, the PI should be prepared to offer a briefing to local, State or EPA Regional officials. The Branch Chief, Division Director, and appropriate Associate Director must be informed of the planned briefing.
- Investigators should seek the advice of local and State officials on the advisability of a community advisory panel and other forms of community

outreach, such as meetings to explain the study and its possible implications to the community as a whole.

- Individual results are reported to the participants as outlined in the informed consent form.
- Decisions to have a community meeting after the results have been analyzed and prior to publication or other public release of information must be made as part of the study planning process. If a public meeting is planned, the PI must inform the Branch Chief, Division Director, and the Associate Director for Health or Ecology of the planned date and give a brief synopsis of the results to be presented. Depending on the classification and/or high visibility of the study, other clearance processes may also be required.

CHAPTER 4

GUIDELINES FOR THE STUDY OF HUMAN TISSUES, INCLUDING IN VITRO RESEARCH

4.1 PURPOSE

This chapter describes the principles and guidelines governing the conduct of human tissues and in vitro studies in NHEERL.

4.2 POLICY

These policies extend the general ones discussed in Chapter 1 into the area of human tissues and in vitro studies. Therefore all policies in Chapter 1 are incorporated by reference in Chapter 4.

4.3 DEFINITIONS

4.3.1 Human Tissue

Any cells, cell lines, fluids, or other biological tissues originally collected from a living person.

4.3.2 Cadaver

A deceased person or portion thereof, including arteries, blood, fluid, or any other tissues from a deceased person. **The Common Rule does not apply to use of tissue from a cadaver.** The Common Rule does apply, however, if portions of an individual, such as tissue or blood, were removed for research purposes while the individual was still alive. For instance, if a participant donated tissue in an earlier protocol for use in future ones, that tissue is not considered to be from a cadaver, regardless of whether the individual has died prior to the current research or is still living.

4.4 CADAVER USAGE

Although not covered by the Common Rule, the use of cadavers is subject to the laws of States, localities, and foreign governments. Any NHEERL Protocol Package involving the use of cadavers must include the following items.

- Copies of relevant laws on procurement, treatment, and disposition of

cadavers. The Uniform Anatomical Gift Act has been adopted in some form in all states and the District of Columbia.

- Documentation indicating that cadavers will be properly and legally procured; that vendors will be informed of the intended use of the cadavers; and that cadavers will be used in a manner consistent with the intent of the donor. Any restrictions by the donor must be honored in the protocol.
- Confidentiality maintained in use of tissue from cadavers.
- Protocol specifying procedures for the treatment, storage, and disposal of cadavers. These procedures must be within accordance of local and State laws, wishes of the donor or next of kin, and must ensure the ethical treatment of the cadavers.

4.5 EXCEPTIONS AND EXEMPTIONS

Before beginning an investigation using either tissue or data obtained from another human study, the researcher must consult with the Director of the NHEERL Human Research Protocol Office to ascertain which of the following three categories best describes the proposed research.

- The research does not fall within the definition of human research and therefore is not covered by the Common Rule.
- The research does constitute human research but is exempt from continuing review as described by the Common Rule.
- The research falls within the definition of human research and is subject to the Common Rule.

4.6 GENETIC TESTING

As with many types of biologic research, the possibility of identifying individuals with a disease susceptibility may occur, especially with the use of genetic testing. Most IRBs have specific requirements for the use of human material in genetic testing. It is best to have a preliminary consultation with an IRB representative to determine the necessary requirements before developing the full Protocol Package. Confidentiality and release of study results are particularly important in these cases.

4.7 STORED SPECIMENS

There are three categories of stored specimens collected in human studies research at

NHEERL: specimens to be stored for as-yet-undesignated tests, but **excluding** genetic tests; specimens to be stored for as-yet-undesignated tests that **may** include genetic testing with personal identifiers accompanying the specimen; and specimens to be stored for as-yet-undesignated tests that **may** include genetic testing with no associated personal identifiers. Each category has specific requirements for protection of the research participant. For additional information and examples of informed consent forms, see <http://www.med.unc.edu/irbCFSAMPAD.DOC>.

CHAPTER 5

GUIDELINES ON THE ETHICAL USE OF NHEERL EMPLOYEES AS RESEARCH PARTICIPANTS

5.1 PURPOSE

Because the protection of all human research participants is an extremely high priority in NHEERL, that same priority must naturally extend to NHEERL employees who experiment on themselves, participate in NHEERL human studies, or request co-workers to take part in these studies.

EPA conducts an extensive health monitoring program on its employees. This Occupational Medical Surveillance Program (OMSP) is not considered human research because its aim is not to create "generalizable knowledge" as defined by the Common Rule. Therefore OMSP is not covered by the Common Rule and or in this document.

5.2 POLICY

These policies extend the general ones discussed in Chapter 1 into the area of use of NHEERL employees as research participants. Therefore all policies in Chapter 1 are incorporated by reference in Chapter 5.

These policies apply to the use of NHEERL employees as research participants, including the provision of biological specimens for methods development.

- NHEERL employees are very strongly discouraged from conducting research on themselves. Alternatives to using NHEERL employees include obtaining participants identified through an appropriate recruitment mechanism and anonymous specimens from internal or external specimen banks. The NHEERL Human Research Protocol Office can advise investigators on how to obtain suitable participants or specimens.
- Employees are not allowed to participate in research that circumvents the IRB process.
- There must be no direct or indirect coercion on employees to participate in NHEERL research projects. Supervisors are not allowed to ask employees they supervise to participate in NHEERL research studies. If NHEERL employees do choose to participate, they are subject to the same precautions as any other research participant to protect the confidentiality of their data.

5.3 ADDITIONAL REQUIREMENTS

NHEERL employees as participants in NHEERL research projects are also subject to the following additional requirements.

- All NHEERL employees must go through the same participant recruitment/screening process required for studies not utilizing NHEERL employees, including the same conditions for inclusion and exclusion for participation.
- The study protocol must contain a statement of the expected number and duration of time periods that NHEERL employees will be expected to spend in the study. A copy of this statement must be provided to the employee. The consent form must appropriately cover the liability issues if the individual participates on his or her own time or on government time.
- An NHEERL participant who feels that his or her rights have been breached or to whom an injury has occurred should contact the Division Human Research Officer, Director of the Human Research Protocol Office, and/or the Chairman of the IRB at the telephone numbers listed in the informed consent form.

5.4 EXEMPTIONS

Because of the very low to non-existent risk of personal injury and the low risk of ethical mistreatment, the procedures outlined below may not need to be subject to the full clearance procedures described in Chapter 1, Section 1.10.1 if they are performed on NHEERL employees. PIs must submit a memorandum requesting an exemption from the Common Rule to the Director of the NHEERL Human Research Protocol Office, who will make the determination of exempt status. Genetic and any other testing that might yield sensitive or unfavorable information cannot be done on any samples collected under this category. In addition, sensitivity to the issue of coercion must still be maintained.

The following sections describe data collection categories that may be exempt from the full clearance procedures when using NHEERL employees. The Director of the NHEERL Human Research Protocol Office may make additions or deletions, as needed.

5.4.1 Biological Samples and Procedures

- Breast milk samples
- Breath collection
- Buccal specimens
- Dermal wipes
- Fecal specimens
- Hair specimens
- Nail specimens
- Nasal lavage
- Non-induced sputum collection
- Saliva collection
- Urine specimens

Note that venous blood samples are **not** included in the above list. Venipuncture is more invasive and can have more significant consequences, physically and psychologically, than the other listed procedures. Many individuals become light-headed or faint when having blood drawn, or can be made anemic with excessive blood drawing. Although employees may donate blood, they must be protected by the same safeguards that apply to other participants.

Also note that semen samples are not included in the above list, because of issues concerning privacy and embarrassment surrounding the collection process.

5.4.2 Other Exempt Procedures

- Routine pulmonary function (spirometry and body plethysmography)
- Blood pressure, pulse oximetry, heart rate variability
- Behavioral Assessment Research System

5.4.3 Survey Questionnaires

For questionnaires taken by NHEERL employees to be exempt from requirements of the Common Rule, the following conditions must be met.

- When employees take questionnaires to evaluate the questions and/or the time needed for completion, individual answers to questions cannot be entered and stored in a database. Only evaluative information, such as suggested changes of wording or format or that it took 30 minutes to complete, can be collected.
- Answers to individual questions from questionnaires may be entered and stored in a database if, and only if, the questionnaires are completely anonymous and employee identity cannot be determined by other means.

APPENDIX A

BELMONT REPORT

The Belmont Report is the cornerstone document on human research ethics in the United States. Completed in 1979 by a group that met at the Belmont Conference Center of the Smithsonian Institution, it embodies three principles: respect for persons, beneficence, and justice.

A.1 RESPECT FOR PERSONS

The first principle recognizes the personal dignity and autonomy of every individual, with special protection for those with diminished autonomy.

- Participants must be given sufficient information to decide whether to enroll, including the purposes of research procedures, risks and anticipated benefits, alternative procedures if therapy is involved, an offer to answer questions, and a statement that they may withdraw from the research at any time without penalty.
- Participants must be able to comprehend the information they are given.
- The consent of participants to enroll must be voluntary.

A.2 BENEFICENCE

The second principle states that investigators have an obligation to protect research participants from harm, to maximize the possible benefits, and to minimize the anticipated risks of harm.

- All possible harms, not just physical or psychological pain or injury, must be considered.
- Risk vs. benefit is based on five principles:

“Brutal or inhumane treatment of human subjects is never morally justified.”

Risks should be minimized, including the avoidance of using human participants if at all possible.

IRBs must be scrupulous in insisting on sufficient justification for

research involving “significant risk of serious impairment.”

The appropriateness of involving vulnerable populations must be justified.

The proposed informed consent process must disclose relevant risks and benefits thoroughly and completely.

A.3 JUSTICE

The third principle requires that the benefits and burdens of research be distributed fairly among members of society.

- The justness of participant selection procedures relates to the participant both as an individual and as a member of social, racial, sexual, or ethnic groups.
- Participants should not be selected simply because they are readily available in settings where research is conducted, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

APPENDIX B

HIPAA TEMPLATE

ADDENDUM TO CONSENT FORM FOR PARTICIPATING IN A RESEARCH STUDY (HIPAA Authorization for use of Protected Health Information)

(NOTE TO INVESTIGATORS: AS YOU COMPLETE THE FORM, DELETE THIS AND ALL OTHER INSTRUCTIONS IN ITALICS)

US Environmental Protection Agency *(may need to include, as appropriate: and the University of North Carolina at Chapel Hill)*

IRB Study Number: _____ *(Leave blank if new submission)*
Version Date of This Form: _____ *(Update for all submissions)*

Title of Study:

Principal Investigator:
UNC-CH Department:
Mailing Address:

Co-Investigators:

Sponsor: *(National Cancer Institute, Name of Pharmaceutical Company, etc)*

What is the purpose of this form?

You have been asked to take part in a research study. The consent form for this study describes your participation, and that information still applies. This extra form is required by the federal "Health Insurance Portability and Accountability Act" (HIPAA). The purpose is to have your permission (authorization) to use health information about you that is created by or used in connection with the research. If you are signing on behalf of someone other than yourself, this permission applies to that person's health records.

What if I don't want my personal health information to be used in this research study?

You may refuse to give this permission. A decision not to sign this form will not change your ability to get health care outside of this research study. However, you may not be able

to participate in this research study unless you sign this permission form. You should discuss this, and any other questions, with the investigators.

Who will be allowed to use my personal health information for this research? And why?

The investigators named above and their assistants will be allowed to see and to use your health information for this research study. We may use it to check on your progress during the study, or analyze it along with information from all other subjects. Sometimes research information is shared with collaborators at other institutions, or with laboratories running additional tests. Your records may also be reviewed by other employees of the US Environmental Protection Agency (*may need to include, the following text or other text, as appropriate: the University of North Carolina at Chapel Hill, representatives of the research sponsor or funding agency, or by the U.S. Food and Drug Administration (FDA), in order to check for quality, safety or effectiveness.*)

What personal health information am I allowing to be used for this research study?

The information we might use includes:

(INVESTIGATORS: READ AND DELETE THESE INSTRUCTIONS. HIPAA requires a "specific and meaningful description" of the information. The description should be as specific as possible but should also be broad enough to cover ALL information that you think you will need during this study.

... supporting information from your entire medical record, results of laboratory tests, x-rays or other images, information from follow-up visits, billing and other financial records, diagnostic codes...

Examples to complete the above section might include:

You may want to refer to the data forms for this study, to see what will be required. If you later need information not covered by this authorization, you will be required to get another authorization to obtain and use that information.)

Where will investigators go to find my personal health information?

We may ask to see your personal information in records at hospitals, clinics or doctor's offices where you have received care in the past. Based on what we know at this time, the places we will seek access to your records include

(INVESTIGATORS: READ AND DELETE THESE INSTRUCTIONS. If known, use the blank to list specific health care providers or health plans at the time of consent. Otherwise, provide a general description of the types of facilities from which you will need protected

health information (e.g. "We will also ask for records from your primary care providers... insurance companies..."). Be aware that some custodians of records may not accept anything other than their own authorization form. Others may accept this form as sufficient if they are adequately identified. This section needs to be sufficiently clear that each health entity to which this form is presented will know that the authorization was intended to apply to it.)

What are the privacy protections for my health information used in this research study?

The federal privacy regulations (HIPAA) apply to personal health information in the records of health care providers and other groups that share such information. There are some differences in how these regulations apply to research, as opposed to regular health care. One difference is that you may not be able to look at your own records that relate to this research study, at least until the study is over. The HIPAA privacy protections may no longer apply, once your personal health information has been shared with others who may be involved in this research.

How long does this permission allow my personal health information to be used?

If you decide to be in this research study, your permission to access and use your health information in this study will not expire, unless you revoke or cancel it. Otherwise, we will use your information as long as it is needed for the study.

What if I change my mind after I give this permission?

You have the right to cancel this permission to use your personal health information for research. In this case, we will not get any more of your health information for use in this research. However, canceling this authorization will not reverse uses of your personal health information that have already happened, or uses that have already been promised and cannot reasonably be reversed. If you want to cancel this permission, you must state your request in writing and deliver it to the Principal Investigator at the mailing address listed at the top of this form. You should clearly state that you want to cancel this permission to use your personal health information in this particular research study. **(Attaching a copy of this form would be very helpful).**

PARTICIPANT'S AUTHORIZATION

I have read the information provided above. By signing this form, I am giving permission for my personal health information to be used in research as described above. I will be given a copy of this authorization form after I have signed it.

_____	_____	_____
Printed Name of Research Subject (or Authorized Representative*)	Signature	Date

_____	_____	_____
Printed Name of Person Obtaining Authorization	Signature	Date

*Only if consent/authorization by someone other than the immediate subject was approved by IRB. If used, also include description of the Authorized Representative's relationship to the subject, and their authority to act on the subject's behalf (parent, legal guardian, etc.).
EPA Version 3-21-03.

APPENDIX C

NHEERL HUMAN RESEARCH SIGN-OFF SHEET

PI (Name/Division):

PROTOCOL TITLE:

NAME OF APPROVING IRB:

IRB-ASSIGNED PROTOCOL NUMBER:

REVIEWS (<i>Attach to EPA Protocol Package</i>)		
Reviewer	Name	Date
Peer Reviewer1		
Peer Reviewer2		
Statistician		
Physician		
Other		
APPROVALS		
Official	Signature	Date
Division Human Research Officer		
Branch Chief		
IRB	<i>(Attach signed approval letter)</i>	
Division Quality Assurance Officer		
Division Director		
NHEERL Human Research Protocol Office Director		
NHEERL Associate Director (for Health or Ecology)		
EPA Human Subjects Research Review Official		

Human Research Guidance

**National Health and Environmental Effects
Research Laboratory**

U.S. Environmental Protection Agency

Second Edition

Draft, April 2005

GLOSSARY

Abbreviation or Acronym

Definition

Co-I	Co- Investigator
DHHS	Department of Health and Human Services
DHRO	Division Human Research Officer
EPA	Environmental Protection Agency
FWA	Federal Wide Assurance
HIPAA	Health Insurance Portability and Accountability Act
HRPO	Human Research Protocol Office
HSR	Human Subjects Research
IRB	Institutional Review Board
NHEERL	National Health and Environmental Effects Research Laboratory
OHRP	Office of Human Research Protections
ORD	Office of Research and Development
PHI	Protected Health Information
PI	Principal Investigator
UNC	University of North Carolina

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CHAPTER 1

INTRODUCTION

1.1 PURPOSE

This document provides guidance to investigators and managers of the National Health and Environmental Effects Laboratory (NHEERL) in the Office of Research and Development (ORD), U.S. EPA on the ethical conduct, review, and approval of all human research activities. The focus of this document is on the methods for ensuring the safety and the rights of human research subjects and on how to conduct such research in a manner consistent with EPA and NHEERL policy. An updated version of the combined NHEERL Human Research Policy and Guidance document of December 18, 2003, this new guidance includes modifications, clarifications, previously omitted material, amplified discussions of topics covered in the new NHEERL Human Research Policy document. (See Section 2.7 for details on the policy document.)

Principal investigators (PIs) responsible for obtaining approval for **human subjects research (HSR)** but who do not have significant experience in HSR at NHEERL should rely on an experienced Co-investigator (Co-I) for guidance in preparing all required documents, obtaining approvals, and conducting the research. If the PI does not have significant HSR experience at EPA, the PI's Branch Chief is responsible for ensuring that a Co-I on the study does have such experience and is available to guide the PI.

1.2 DOCUMENT OVERVIEW

Chapter 2 gives a brief overview of the regulatory framework under which all HSR is conducted at NHEERL and reviews some of the history of HSR and the context in which such research is conducted today. Chapters 3 and 4 describe the Common Rule (40 CFR 26) and the EPA implementation of the Common Rule (EPA Order 1000.17, Change A1), respectively. These chapters also interpret specific aspects of these policy documents as they apply to HSR in NHEERL. Chapters 5 through 9 detail specific guidance for complying with the NHEERL Human Research Policy. Chapter 5 describes the requirements and the process for review, approval, and ongoing oversight of all human research activities conducted by or supported by NHEERL. Chapters 6 through 9 give additional guidance specific to controlled-exposure studies, epidemiology studies, in vitro studies, and research using NHEERL employees as subjects.

1.3 NHEERL HUMAN RESEARCH PROTOCOL OFFICE

The Director of the NHEERL Human Research Protocol Office (HRPO) is responsible for the ethical oversight of all HSR and for coordinating the entire process by which all human research activities in NHEERL are reviewed and approved. The duties of this office are as follows.

- Ensuring that the safety and rights of all human subjects are protected.
- Advising NHEERL investigators in the preparation of HSR protocols that are consistent with this guidance document and with EPA, ORD, and NHEERL policy.
- Assisting NHEERL investigators and managers in understanding their responsibilities for conducting HSR in NHEERL
- Maintaining the official records for HSR in NHEERL.

Although the Division Human Research Officer (DHRO) should be consulted for any questions about the preparation or approval of HSR protocols, the HRPO Director must be contacted before a study protocol is developed involving human data of any kind.

CHAPTER 2

HISTORICAL OVERVIEW OF POLICIES REGULATING HUMAN SUBJECTS RESEARCH

The conduct of human research carries special responsibilities with regard to ethical, medical, and scientific issues. Society, while generally in favor of research on humans, has imposed special requirements on investigators because of concern about mistreatment of human research subjects based, in part, on the historical legacy of improper human studies.

The following sections summarize key documents tracing the profound changes in human research ethics that took place from immediately after World War II to the present and identifies the additional policy documents that currently govern the conduct of HSR at NHEERL. More detailed descriptions and guidance regarding these policy documents are provided in Chapters 3, 4, and 5.

2.1 NUREMBERG CODE (1947)

The Nuremberg Code was a direct result of post-World War II war crimes trials of Nazi physicians who committed atrocities on prisoners of war under the guise of medical research. The first principle of the Code is, "The voluntary consent of the human research subject is absolutely essential."

2.2 DECLARATION OF HELSINKI (Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964, and amended by the 29th World Medical Assembly Tokyo, Japan, October 1975; 35th World Medical Assembly Venice, Italy, October 1983; and the 41st World Medical Assembly Hong Kong, September 1989)

The Declaration of Helsinki is the most universally accepted human research document. It has been amended numerous times to keep up with the changing research world. In the case of EPA human research conducted in foreign nations, adherence to the Declaration of Helsinki is the strongest assurance that investigators will conform to an accepted international norm to protect human subjects.

2.3 BELMONT REPORT (1979)

The Belmont Report is the cornerstone of U.S. human research ethics documents and is the foundation upon which the Common Rule is based. The report was completed by a group that met at the Belmont Conference Center of the Smithsonian Institution. It embodies three principles - respect for persons, beneficence, and justice.

**2.4 “COMMON RULE” (Federal Policy for the Protection of Human Subjects)
[codified by EPA, 40 CFR 26] (1991)**

The Common Rule was enacted to bring uniformity and cohesion to a patchwork of existing Federal human research protections. It has been ratified by 17 Federal agencies and departments, hence the name “Common Rule.” It embodies and expands on the principles of the Belmont Report. The Common Rule establishes minimum standards for the conduct of HSR funded by the Federal government. Federal agencies and departments can require stricter standards for human research (as EPA does), but cannot weaken the Common Rule requirements. Common Rule principles, however, have become the de facto standard for much of the human research conducted in the United States, including human research not federally funded.

The Common Rule consists of four subparts. Subpart A covers requirements for all human research, and comprises 40 CFR 26 as codified by the EPA. Subparts B, C, and D provide additional protections for classes of individuals considered especially vulnerable. Subpart B covers research involving pregnant women, fetuses, and neonates; Subpart C, research on prisoners; and Subpart D, research on children – a topic of increasing concern to the Agency. These latter three subparts are not included in 40 CFR 26. All four subparts are included, however, in 45 CFR 46 as codified and revised by the Department of Health and Human Services (DHHS) in 2001. Although Subparts B, C, and D are not formally included in EPA regulations, they are widely accepted and NHEERL policy requires that research on all four classes of vulnerable populations be in compliance with these regulations.

The types of research that are subject to the Common Rule and exempt from the Common Rule are discussed in detail in later chapters of this document.

2.5 EPA ORDER 1000.17, CHANGE A1 (1999)

This EPA policy formally implements the Common Rule and imposes further conditions on all HSR conducted in or supported by the Agency, and therefore it applies to NHEERL. This Order specifies that EPA cannot conduct or support any HSR unless it has been approved by the Agency Human Subjects Research Review Official (HSRRO). Everyone in the Agency involved in or supervising those involved in human research must be familiar with this Order.

See http://www.epa.gov/oamrtpnc/forms/1000_17a.pdf for additional information.

2.6 HIPAA (HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT) (2003)

HIPAA, which became effective in April 2003, includes both the portability of employees' health insurance as employees change jobs (which does not affect HSR at NHEERL) and the accountability for individual Protected Health Information (PHI)(which does).

HIPAA recognizes three "covered entities"—health care providers, health care information clearinghouses, and health care payers – that must have authorizations from individual patients or research subjects before their PHI can be shared and used in research. Because NHEERL is not a covered entity, it ordinarily does not have to comply with HIPAA. However, if human studies are conducted jointly by NHEERL scientists and any type of covered entity, such as the School of Medicine of the University of North Carolina at Chapel Hill, HIPAA authorization may be required from each of the study subjects. The Institutional Review Board (IRB) of record for the participating covered entity is a good source of information as to whether HIPAA is required. Other situations that do not require prior HIPAA authorization from study subjects include studies on existing data bases, studies conducted in foreign countries, and studies on deceased persons.

2.7 NHEERL HUMAN RESEARCH POLICY DOCUMENT (2004)

The formal NHEERL Human Research Policy document imposes requirements for the conduct or support of HSR beyond those required by 40 CFR 26 and by EPA Order 1000.17, Change A1. In particular, it specifies the required contents of the HSR protocol package that must be initially prepared for each study and identifies the responsibilities of those who must review and approve the document. It also establishes bioethics training requirements for NHEERL employees engaged in HSR and establishes policies for record keeping. Chapter 5 of this guidance document covers these subjects in detail.

CHAPTER 3

THE COMMON RULE (40 CFR 26)

As described in Chapter 2.4, the Common Rule consists of four subparts. EPA's current codification of the Common Rule (40 CFR 26) includes only Subpart A, which describes the basic policy for protection of human subjects. EPA's implementation of the Common Rule, EPA Order 1000.17, Change A1, found at http://www.epa.gov/oamrtpnc/forms/1000_17a.pdf, contains the Common Rule as Appendix A. Subparts B, C, and D, which provide for the protection of classes of vulnerable subjects, is covered in 45 CFR 46, the version of the Common Rule codified by the (DHHS) and found at the Web site of the DHHS Office of Human Research Protections (OHRP): <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>.

The Common Rule is a well-written but densely packed document containing information about the requirements for approval, conduct, and oversight of HSR. Some of the most relevant information for NHEERL investigators is summarized below, in the order in which it appears in the Common Rule and with the section headings used in the Common Rule. This summary is not intended to be comprehensive. NHEERL investigators conducting HSR are responsible for being familiar with all requirements of the Common Rule and for conducting research in accordance with it.

3.1 SECTION 26.101 - TO WHAT DOES THIS POLICY APPLY?

This section states that the Common Rule applies to all research involving human subjects conducted or supported by EPA or other Federal agencies that have adopted the Common Rule. A list of research activities that are exempt from the Common Rule is included. The exempt category most likely to be encountered by NHEERL employees is research on existing human data or tissues publicly available or recorded so that subjects cannot be identified either directly or through identifiers linked to them. That is, HSR using data or tissues recorded in a completely anonymous format may be exempt. **Only the Agency HSRRO, along with the IRB of record for the organization conducting the research, can make the final determination of exempt status for HSR. NHEERL investigators cannot make that decision themselves.**

3.2 SECTION 26.102 - DEFINITIONS

This section defines a number of terms, the two most relevant of which are "research" and "human subject". Quoted material is from the Common Rule; bold facing has been added here for emphasis.

“Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to **generalizable knowledge**. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes.”

“Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.”

Between them, Sections 26.101 and 26.102 establish which studies are governed by the Common Rule. Currently, most NHEERL studies involving human data or tissues clearly fall within the definition of HSR under the Common Rule because they meet the definition of research, involve intervention or interaction with a subject, or clearly involve analysis of data with personal identifiers. There are a number of other situations, however, where it is not immediately apparent that a study constitutes HSR.

Often at issue is whether personally identifiable information is available to the investigator. Clearly, analysis of existing data that is publicly available and that cannot under any circumstances be linked to individuals is not HSR under the definitions in the Common Rule. However, there is the large gray area of existing data sets that do not contain personally identifying data but which can be linked to individual subjects through coded identifiers. If desired, an investigator knowing the code conceivably could learn the identity of subjects by acquiring personally identifying data such as address, birth date, or social security number.

Likewise, it is not always clear whether research on human cell lines is HSR. That often depends upon the circumstances under which the tissue is obtained and the measures in place to protect the identity of the source of the tissue. **A decision about whether a given study involving human data or tissue meets the definition of HSR must never be made by the investigator or the DHRO alone but must be made in consultation with the HRPO Director.**

3.3 SECTION 26.103 - ASSURING COMPLIANCE WITH THE COMMON RULE

This section requires that any research conducted or supported by any Federal agency or department must be reviewed by an appropriate IRB, and that any organization engaged in such research must have written assurances in place indicating its compliance with requirements of the Common Rule. In most cases, this assurance is provided by DHHS issuing a Federal Wide Assurance (FWA) to the organization.

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The Human Studies Division (HSD) of NHEERL has an FWA that identifies the IRB of the University of North Carolina at Chapel Hill (UNC) as its IRB of record. Investigators from other NHEERL divisions who collaborate on HSD studies are covered under the HSD FWA.

Investigators from NHEERL divisions other than HSD who collaborate with another institution, such as the Centers for Disease Control and Prevention or the National Cancer Institute that have an existing FWA, may be covered by the other institution's assurance at the discretion of that institution. As another option, the other institution could require NHEERL investigators to obtain an FWA from DHHS for the particular study.

An additional option for NHEERL health and ecology divisions without their own FWA is to contract with a commercial IRB that has a FWA and that agrees to review and provide oversight for an individual HSR project.

3.4 SECTION 26.109 - IRB REVIEW OF RESEARCH.

This section indicates that an IRB will review research covered under the Common Rule, will approve or disapprove of such research, and will require re-approval at no more than yearly intervals. It also specifies that the IRB will require informed consent consistent with Section 26.116 of the Common Rule and shall require documentation of informed consent. Additional information on the role of IRB review and the other basic guidance on informed consent are listed below.

- Section 26.111 Criteria for IRB approval of research
- Section 26.112 Review by institution
- Section 26.113 Suspension or termination if IRB approval of research
- Section 26.114 Cooperative research
- Section 26.116 General requirements for informed consent
- Section 26.117 Documentation of informed consent
- Section 26.124 (Additional) Conditions

CHAPTER 4

EPA ORDER 1000.17, CHANGE A1 (1999)

EPA Order 1000.17, Change A1 establishes policy for all HSR conducted by or supported by the Agency. All HSR conducted in NHEERL must be compliant with this policy. It requires that all studies meeting the criteria for HSR as defined in the Common Rule (40 CFR 26) must comply with the Common Rule and, in addition, must be either approved by the Agency HSRRO or determined by that official to be exempt from the Common Rule. Note that the only person in the Agency authorized to make a determination of exempt status for EPA is the Agency HSRRO. Even if an IRB labels a study as exempt, the protocol must be submitted to the HSRRO for the final determination. This policy presumes that any study involving risk of potential substantial injury or irreversible health effects resulting from the study will not be approved, regardless of whether it is consistent with the Common Rule.

The Policy also defines several terms, including "Human Subject" and "Research", which are taken from the Common Rule. It also requires foreign studies not governed by the Common Rule to obtain approval from the HSRRO, and requires all EPA employees to report any known or unexpected harm to one or more human subjects associated with EPA-conducted or EPA-supported research to the Agency HSRRO.

In the event of injury to a subject on any HSR conducted in NHEERL, the PI must immediately suspend the study and report the incident to the HRPO Director, Division Director, and IRB of record. The HRPO Director will immediately initiate communication of the event up the chain of command to the Agency HSRRO.

CHAPTER 5

DEVELOPMENT, REVIEW, AND APPROVAL OF HUMAN SUBJECTS RESEARCH PROTOCOLS

The NHEERL Human Research Policy document, the companion to this guidance document, imposes requirements for the conduct or support of HSR by NHEERL beyond those that are required by EPA Order 1000.17, Change A1 and by 40 CFR 26. In particular, the policy specifies the required contents of the HSR protocol package that must be prepared for each study and identifies the responsibilities of those who must review and approve the package prior to approval by NHEERL management. It identifies policy for research conducted on vulnerable populations and indicates that an HSR study with a PI who has little experience conducting NHEERL HSR must also include a Co-I with such experience, who is available to provide guidance to the PI. It also establishes training requirements for NHEERL employees engaged in HSR and establishes policies for record keeping.

5.1 PURPOSE

This chapter of the guidance document interprets the NHEERL Human Research Policy and serves as a "How to" manual for the preparation and initial reviews of the protocol package, as well as the conduct and ongoing oversight of approved studies.

5.2 REQUIREMENTS FOR HUMAN SUBJECTS RESEARCH

All HSR requires the preparation of a protocol package for review by NHEERL and EPA management but the specific requirements for the protocol package and the level of review depend upon the type of study proposed.

The first decision to be made for getting approval for any research activities in which data or samples of human origin are involved is whether the proposed study meets the definition of HSR discussed in Chapter 3 and in Section 26.102 of the Common Rule. The study must be consistent with the definitions of research and human subject (see Section 3.2). This determination may not be made independently by the PI or the Division HRO but must be made by the HRPO Director. If necessary, the HRPO Director will also consult the Division Director and/or the IRB of record. Human research activities that are determined not to meet the definition of HSR undergo an abbreviated approval process described in Section 5.5. All other human research activities that meet the definition of HSR, including studies determined to be exempt from the Common Rule, must be consistent with the following guidance.

Any research activity that meets the definition of HSR and is conducted by or supported by NHEERL must comply with the Common Rule (40 CFR 26), EPA Order 1000.17, Change A1,

and the NHEERL Human Research Policy. This research includes studies conducted by NHEERL investigators; supported by NHEERL through funding or the provision of facilities and services (e.g. through cooperative agreements, contracts, or grants); and funded by other organizations and conducted elsewhere, for which an NHEERL employee acts as a collaborator or is otherwise engaged in HSR.

In addition to meeting EPA requirements, all NHEERL investigators engaged in HSR must also meet all of the initial and ongoing requirements of any Institutional Review Board (IRB) that has jurisdiction over the study. The UNC IRB, the IRB of record for HSD, must approve all such studies or reach an agreement to defer to another IRB.

The contents of the protocol package and the review process for typical HSR studies are described in Sections 5.3 and 5.4. Non-typical exceptions are discussed later in this chapter.

5.3 TYPICAL NHEERL HUMAN SUBJECTS RESEARCH PROTOCOL PACKAGE

This section describes the contents of a protocol package prepared for a typical NHEERL study. The package serves several key functions. In addition to including the study protocol, consent form, and any other documents required for review by an IRB, it also contains reviews addressing the scientific merit and the potential risks and benefits of the study; a Study Justification Document showing why the Agency should support the proposed research; and a Fact Sheet summarizing the importance of the study in non-technical terms for upper EPA management and the general public.

The complete package is assembled stepwise prior to review by the NHEERL Associate Laboratory Director for Health or Ecology and the Agency HSRRO. Descriptions of the individual components of the package are presented below in the approximate order in which they are prepared. A step-by-step guide to the order of preparation and review of the package is presented in Section 5.4. Some of the elements (research protocol, consent form) are prepared according to IRB specifications while others are prepared according to EPA specifications. Information about any element of the EPA protocol package can be obtained from the HRPO.

5.3.1 Research Protocol

The research protocol is prepared according to the instructions of the IRB that will ultimately review the protocol. A template of the protocol application form and other forms required by the IRB of the University of North Carolina at Chapel Hill is found at <http://ohre.unc.edu/forms.php>. Staff members of the Medical Station and the recruitment office should be listed under "...all other project personnel..." on the first page of the IRB application. All individuals listed on the protocol application must meet the training requirements specified by the IRB and NHEERL, as described in Section 5.3.4. Organizational affiliations should be listed for all investigators and study staff.

Particular attention should be paid to the following sections in the UNC IRB protocol application form. For Section A-4 5, "Full description of risks and measures to minimize risk", in addition to a comprehensive description of any physical risk to subjects and the measures to reduce them, the protocol should clearly state how personally identifying information will be handled, who will have access to it, and how it will be protected. When possible, samples should be coded without personally identifying information. Data without personal identifiers should only be identified by code. Access to personally identifying information and the link between personal identifiers and the codes should be limited to as few people as possible and should be secured. For Section A-4 6, "Data analysis", the investigator should provide evidence that the study has adequate power to answer the question of interest. Because the Common Rule requires that "risks to subjects are reasonable in relation to anticipated benefits...", such a judgment cannot be made without accurate assessment of the potential benefits. Any procedures and risks to subjects listed in the protocol must also be included in the consent form.

5.3.2 Consent Form

Informed consent is a process, not just a form. Information must be presented to enable potential subjects to decide voluntarily whether to participate as research subjects. Informed consent is the fundamental mechanism to ensure respect for persons through provision of thoughtful consent for a voluntary act. The procedures used to obtain informed consent should be designed to educate the subjects by using language that they can understand. Therefore, informed consent language and documentation, especially the explanations of the study purpose, duration, experimental procedures, alternatives, risks, and benefits must be written in "lay language". The consent form is used to document the basis for consent, the subjects' indication of consent, and as a written reference for the subjects.

The process of obtaining informed consent, the required elements of a consent form, and the documentation of informed consent must be consistent with 40 CFR 26, Sections 116 and 117 of the Common Rule, listed in Section 3.4 of this guidance document. In almost all cases, the IRB of record will provide a template for the consent form that is consistent with the Common Rule, and the investigator should follow the guidelines of that IRB. Additional information is available at the Web site of the DHHS Office for Human Research Protections (OHRP) at (<http://www.hhs.gov/ohrp/policy/index.html#informed>).

In addition to the requirements of the IRB of record and the Common Rule, there are EPA and NHEERL requirements for the consent form that must be met. Under the section "What will happen if you are injured by this research?" the existing statement in the UNC IRB template must be modified to read as follows.

"Neither the University of North Carolina at Chapel Hill nor the U.S. EPA has set aside funds to pay you for any such reactions or injuries, or for the related medical care. If you believe you have suffered a research-related injury, you have the

right to pursue legal remedy if you believe that your injury justifies such action. The Federal Tort Claims Act, 28 U.S.C. S 2671 et seq., provides for money damages against the United States when property loss or personal injury results from the negligent or wrongful act or omission of any employee of the EPA while acting within the scope of his or her employment. Signing this consent form does not waive any of your legal rights or release the investigator, the sponsor, the institution, or its agents from liability for negligence. If a research-related injury occurs, you should contact the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217."

Under the section "What if you have questions about your rights as a research participant?" the last sentence must be amended to read as follows.

"If you have any questions or concerns regarding your rights as a research subject, you may contact the Chairman of the IRB Committee at 919- 966-1344 and/or the Director of the EPA NHEERL Human Research Protocol Office at 919-966-6217."

If an investigator anticipates obtaining information about a subject that has a bearing upon the subject's health or safety (such as an elevated blood lead level) or if the investigator is required by law to report to the authorities (such as suicidal ideation in a minor subject) the consent form should specify how these topics will be handled.

5.3.3 Other Required Items

Complex investigations often require a wide range of additional items that must be reviewed and approved by the IRB and by EPA. Some common examples include recruitment brochures, advertising, questionnaires, and surveys. Depending on the number of individuals to be contacted, surveys may also have to be approved by the Office of Management and Budget (OMB) for an estimate of burden to the subjects. The protocol package must contain all documents required by any reviewing organization.

5.3.4 Ethics Training Requirements

All NHEERL investigators conducting HSR must have formal human research training that is updated annually. Although providing proof that **all** study personnel have ethical training is relatively new, it is by no means unique to NHEERL. The spirit of this requirement is that everyone who is engaged in the planning, conduct, or analysis of HSR understands how to treat subjects ethically, safely, and confidentially. Many universities and government research groups now require that any study staff member who has direct contact with study subjects or with personal identifying information undergo appropriate ethics training. However, this does

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not imply that every single individual that has any contact whatsoever with a study subject has to go through a full, formal, certifiable training process.

Undoubtedly, there will be variability from one IRB to another in the oversight and enforcement of this requirement. With regard to the UNC IRB, each of the its eight IRB committees – four in Biomedical, and one each in Dental, Public Health, Nursing, and Behavioral – is empowered to question the level and type of ethics training that personnel should have to ensure ethical conduct for a particular study. Hence, the specific guidelines and requirements may very well be different from one protocol to the next, especially with regard to questions about the level and type of ethics training for “ancillary” support staff. Some examples of ancillary personnel may include contracted transportation providers, local volunteers administering surveys or otherwise assisting in handling subjects at a study location, receptionists registering subjects, etc. Ancillary personnel present no more than minimal risk to the subject and this risk usually comes in the form of potential breach of confidentiality.

Broad ethics training requirements may particularly impact studies with large size, studies conducted at distant and/or multiple locations, or studies with complex logistics. A general guiding principle is that the PI must be prepared to explain the plan or rationale to the IRB regarding the issue of ethics training for ancillary staff. This could be done in the form of memorandum accompanying the other training certificates for the principal study staff. The following specific guidelines will make it more likely that reviewers are convinced that NHEERL researchers are taking this responsibility seriously.

- Any UNC-affiliated or HSD-affiliated study personnel need to show evidence of Collaborative IRB Training Initiative (CITI) ethics training at <http://www.citiprogram.org/default.asp>
- Major contractors who are involved with the planning, conduct, and data analysis of a study need to show evidence of ethics training. For contractors with numerous employees, the IRB may accept a blanket letter that details the contractor's role in the study and what type of ethics training is provided by that contractor to its employees. Because the type and extent of involvement of contractors will vary significantly from one contractor to another, the PI should discuss the issue with the Branch Chief and the HRPO Director to increase the chances of IRB acceptance.
- For the broad range of other individuals who might be considered ancillary support, either of the following options is available in lieu of formal ethics training.
 - ✓ Provide an "Oath of Confidentiality" statement for the ancillary staff

member to sign that serves as a pledge that he/she will keep subject information confidential.

- ✓ Develop and provide an IRB-approved brochure to the ancillary support staff member to sign that covers the basics on the ethical management of study subjects.

Currently, those individuals who only analyze specimens without personal identifying information do not need to show evidence of ethics training.

5.3.5 Initial EPA Reviews

These reviews are conducted to ensure the scientific soundness of the proposed study and to identify any relevant safety or risk issues. The Branch Chief decides which, if any, of these reviews are required. They might include reviews by statisticians, scientists, or medical personnel, among others. Written responses by the PI to all reviews must be included in the protocol package for EPA review. Reviewer comments and PI responses must also be submitted for IRB review of controlled-exposure studies discussed in detail in Chapter 6.

5.3.5.1 Extramural Scientific (Peer) Reviews—

Prior to submitting a protocol to the IRB, the PI is responsible for obtaining any EPA-required reviews by technical experts outside the PI's Division. At a minimum, the reviewer should be provided draft copies of the protocol and the consent form. The primary objectives of the reviews are to obtain comments on the following topics.

- Scientific merit.
- Value added by conducting human research rather than animal or in vitro research. (This requirement may not be applicable to some epidemiological studies.)
- Any concerns regarding issues of the ethical and safe treatment of study subjects.

The number of required reviews depends first on whether the subjects are deliberately exposed to any chemical, physical, or biological agent and then on the size and purpose of the study. Any study, whether pilot or full-scale, that deliberately exposes subjects to such agents requires at least one extramural scientific review. Full-scale, controlled-exposure studies of subjects to agents that are known pollutants require two external reviews. Full-scale epidemiologic studies with no deliberate exposure of subjects to agents require one external review.

Pilot studies not involving controlled exposure are treated on a case-by-case basis regarding external reviews requirements. Based on what specifically is being piloted, the PI, Branch Chief, and Division HRO may need to jointly decide on the need for external reviews. If consensus cannot be reached, the HRPO Director will make the final decision.

These reviews must be formal, written comments by experts in the field.. The PI should provide a written response to each comment in the review, indicating whether the changes suggested by the reviewer have been made, and if not, why not. The reviewer will be chosen by the PI's first-line supervisor. In some cases, reviews conducted by or required by outside collaborators, funding agencies, or regulatory bodies such as the Federal Drug Administration (FDA) and the National Institutes of Health (NIH) may serve this purpose if they address the required elements of the review. For collaborative studies involving UNC, reviews provided by the General Clinical Research Center may serve as an external review.

5.3.5.2 Medical Review--

As discussed in detail in Chapter 6, all human studies that involve controlled exposure to pollutants must be reviewed by a physician. Similarly, any study using procedures that involve significant physical risk to subjects (e.g. bronchoscopy, methacholine challenge) must also be reviewed by a physician. The review must address the following elements.

- Known risks inherent in the exposure and any procedures to be conducted have been identified in the protocol.
- Known risks specific to the proposed study population have been identified.
- Appropriate measures to reduce risk are in place.
- Appropriate medical criteria are in place for selection of the proposed study subjects.
- The investigative team and the medical staff are qualified to deal with any adverse medical events that could reasonably be anticipated to arise.

The physician must be identified as a reviewer on the NHEERL sign-off sheet. A physician-PI cannot review his or her own study. A physician Co-I, however, may provide the medical review. Any concerns identified by the physician should be resolved in discussions with the PI or with the PI and the HRPO Director.

5.3.6 Fact Sheet.

A Fact Sheet provides a brief summary of any high-visibility issue, project, or activity to the

Assistant Administrator of the Office of Research and Development (ORD) and, when warranted, to the Administrator. Most NHEERL projects involving human research will require a Fact Sheet. The Branch Chief, in consultation with the Division Director, will determine whether a Fact Sheet is required.

Fact Sheets, although for internal EPA use, are written in a non-technical, jargon-free style because information from Fact Sheets may also be used by the EPA Office of Public Affairs and by Regional and Program Offices to disseminate information about Agency research projects to interested parties, including the general public.

Fact Sheets are required at the beginning of a research project and may be required at other stages of the project. The Branch Chief, Division Director, and the NHEERL communications office can be consulted regarding these requirements. The Fact Sheet must be no more than one page in length and written in a standard format shown below. A draft Fact Sheet is included with the protocol package. The HRPO can assist investigators in preparing Fact Sheets and maintains a complete file of Fact Sheets for reference and review. In parallel, the draft Fact Sheet must be also submitted to the NHEERL communications office, which will assist the PI, if necessary, in tailoring the language to a lay audience. The NHEERL communications office then sends a final copy of the Fact Sheet to ORD senior management, as appropriate.

The Fact Sheet must include the following five categories.

- Impact Statement:** Explain why this research is important to the Agency, emphasizing the benefits to be gained by the Agency.
- Background:** Explain why this research is being conducted.
- Study Description:** Provide a brief, non-technical description.
- Timeline:** Include projected starting and closing dates, and current status of IRB and EPA reviews.
- Contact:** Give name, NHEERL Division, and telephone number of contact person.

5.3.7 Study Justification Document.

Every protocol must be accompanied by a Study Justification Document, which the PI prepares specifically for the Associate Director for Health or Ecology, as appropriate. The study is justified on the basis of ethical considerations such as risk to the subject against the anticipated benefits to the subject or to society. Because there is little or no benefit to the individual subjects

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in most human studies, it is critical to balance the potential risks to subjects against the importance of the study. Many human exposure studies entail negligible risk. But as the risk to subjects increases, the potential benefit of the study to EPA and to society must be more compelling. In all cases, the risk to the research subjects must be minimized and fully disclosed with the following issues addressed explicitly.

- Relevance of the research to the Agency's mission.
- Clear justification of the value added by human studies, emphasizing why existing animal or tissue studies are insufficient for this particular research.
- Value added to society in the form of anticipated public health benefit.
- Value added to decision-making in the form of scientific merit.
- Subject safety, including the following topics.
 - ✓ Risks to subjects are minimized by careful planning and design.
 - ✓ Risk assessment calculations, if any, are summarized from the protocol.
- Certification that all NHEERL researchers who administer tests, collect data from subjects, handle confidential information, or are otherwise listed on the protocol are compliant with the latest NHEERL requirements for investigator education.
- Detailed communication strategy for reporting study planning and results to interested parties such as EPA Regions and the communities that participated in the study, if appropriate. (The strategy for communicating results to the subjects is described in the informed consent form.) The anticipated time-frame for distribution of results must be included.
- Reference must be made to written reviews by extramural scientific reviewers that address the above points and that are included in the protocol package.

Following the bulleted format outlined above may expedite the review and approval process, especially for complex studies.

5.3.8 Cover Memorandum

The PI should prepare a memorandum to the NHEERL Associate Laboratory Director for Health or Ecology requesting review of the protocol. It should very briefly describe the study and the

role of NHEERL in the study and should list the complete contents of the accompanying protocol package described in Section 5.3.10.

5.3.9 NHEERL Sign-off Sheet

A copy of the sign-off sheet can be obtained in Appendix A, by e-mail from the HRPO, or on the HSD intranet home page: <http://rthsd.herl.epa.gov/hsd/>, then click on Protocol Reference Library. The names of all reviewers should be typed or printed and approving officials should sign the sheet.

5.3.10 Complete Protocol Package

The final complete protocol package consists of the following. **Two complete paper copies** must be prepared and delivered to the HRPO prior to review by the NHEERL Associate Director for Health or Ecology and by the Agency HSRRO. **The package should be arranged in the following order.**

- Cover memo from the PI to the Associate Laboratory Director for Health or Ecology requesting review of the protocol.
- NHEERL sign-off sheet with signatures.
- NHEERL Fact Sheet.
- NHEERL Study Justification Document.
- IRB approval letter(s).
- Research protocol as approved by the IRB.
- Consent forms approved and stamped by the IRB.
- Questionnaires and advertising approved and stamped by the IRB.
- Ethics training reports required by the IRB.
- Copies of extramural scientific reviews and responses.
- Copies of medical, statistical, or other required reviews and responses.

Most HSR conducted by NHEERL employees or conducted in NHEERL facilities under contract or cooperative agreement will require preparation of this package. A description of the order in

which these documents should be prepared and reviewed is presented in the next sections.

5.4 REVIEW AND APPROVAL PROCESS OF A TYPICAL NHEERL HUMAN SUBJECTS RESEARCH PROTOCOL PACKAGE

The entire NHEERL Human Research Protocol Package is prepared and reviewed in stages by the IRB and EPA. All required reviews and responses are obtained in writing and approvals are recorded on the NHEERL sign-off sheet. A more complete description of the individual elements is given in preceding sections of this chapter. See Appendix B for flow diagram.

Step 1. Protocol Preparation.

Following the instructions of the applicable IRB, the PI and Co-Is prepare drafts of the protocol and the informed consent form. The PI presents the proposed study to interested parties, such as the technical staff, other scientists, medical and recruitment staffs, statisticians, DHRO, Division Quality Assurance (QA) Officer, Dosing Review Officer (if a dosing study) and Branch and Division management for comment. The PI then incorporates any necessary changes into the protocol and the informed consent form.

Step 2. Initial Reviews.

After revisions of the protocol and consent form, the PI must obtain any required medical, statistical, and other written reviews required by the Branch Chief. The PI must then provide written responses to the reviewers' comments and revise the protocol, if necessary.

Step 3. Peer Reviews.

In most cases, the protocol and informed consent form will require written scientific review from experts external to the PI's Division, who are selected by the PI's first-line supervisor. The PI must provide written responses to the reviewers' comments and revise the protocol and informed consent form as needed. For controlled-exposure studies the UNC IRB has requested, and NHEERL requires, that peer reviewer comments and NHEERL responses be sent to the IRB with the protocol.

Step 4. Branch Chief and Division Review.

The Branch Chief and DHRO must review and approve the protocol, informed consent form, and all other items to be sent to the IRB **before** the PI sends these items to the IRB. A hard copy of the complete package to be sent to the IRB

should be provided for these EPA reviews. For all studies in which pollutants or diagnostic materials are administered to subjects, the dosing procedure outlined in the protocol and informed consent form must be reviewed by a qualified Dosing Review Officer designated by the Division Director. The Dosing Review Officer in HSD, currently the HSD QA Officer, performs a preliminary dosing review prior to submission to the IRB. This pre-IRB review allows early identification of items that would have to be changed later to meet EPA requirements. This early dosing review may also prevent the need for later amendments to the protocol or consent form. After IRB approval, the Dosing Review Officer provides a formal review in Step 6.

Step 5. IRB Approval.

Only after the above steps are completed can the PI send the protocol, informed consent forms, peer reviews and responses, and any other information required by the IRB to the IRB for review and approval. See the UNC IRB Intranet site <http://ohre.unc.edu/forms.php> for current instructions for submission of applications. In addition to the completed protocol application and consent form, the UNC IRB currently requires proof of ethics training for all investigators having contact with human subjects or their personally identifiable specimens or data, and copies of all advertising, questionnaires, and surveys. The PI must notify the Branch Chief and DHRO if significant alterations to the initially submitted protocol were required by the IRB as a condition of approval.

Step 6. EPA Administrative Approval.

After IRB approval, the PI compiles a complete protocol package that is then reviewed and approved by the Division QA Officer for assurance that EPA QA standards for HSR are met. If applicable, the Dosing Review Officer reviews and approves the dosing procedures. The package is next reviewed and approved by the Division Director. If any changes in the protocol or consent form are required during this portion of the EPA review process, the amended protocol must be resubmitted to the UNC IRB for approval.

After all approvals are received, the PI must give two complete paper copies of the final approved protocol package (see Section 5.3.10) to the HRPO Director who reviews the package for accuracy and completeness, then sends one copy of the complete Protocol Package to the Associate Director for Health or Ecology and keeps a second copy for the official Agency files. Upon approval, the Associate Director forwards the protocol package to the Agency HSRRO for final Agency review and approval.

Step 7. Study Commencement.

Actual recruitment and study of human subjects can begin only after the Agency HSRRO sends a memorandum of approval to the HRPO Director and to the PI, who must distribute copies to the Branch Chief, Division Director, DHRO, and the Medical Station, if applicable.

Step 8. Record Keeping.

The HRPO maintains the official Laboratory file for approvals and ethics oversight of all HSR projects. Following initial approval, the PI must ensure that the HRPO is given copies of all documents needed to maintain a complete and current file, including copies of all cover letters, protocol amendments and renewals, current stamped consent forms, questionnaires, and advertising materials, reports of adverse events, IRB approval letters, and any other correspondence with the IRB regarding the study. In short:

“If you send it to the IRB, simultaneously send a complete copy to HRPO.

If the IRB sends it to you, immediately send a complete copy to HRPO.”

5.5 PROTOCOL REVIEW PROCEDURES FOR SPECIAL CASES

The procedure for preparation, review, and approval of HSR may differ from that specified above in the following special cases.

5.5.1 Studies Not Meeting the Definition of HSR

Before beginning an investigation using either data or tissue involving human subjects, the investigator must consult the HRPO Director to determine whether the proposed research is subject to the Common Rule. The rules governing that decision are very complex. Some studies will be considered HSR and therefore are subject to the Common Rule and require a complete protocol package. Other studies may be similar except for a slight nuance but may not be HSR. Therefore they are not subject to the Common Rule and do not require a typical protocol package.

No protocol package is required for human research activities that do not meet the definition of HSR. Instead, the PI's Division Director must write a memo to the HRPO Director describing the study and the reasons why the proposed research is not HSR. The NHEERL HRPO must concur in writing before such research can proceed. In the event of uncertainty as to whether a study is HSR, further consultation with the IRB of record and/or the Agency HSRRO will be undertaken.

5.5.2 Exempt Studies and Waiver of Informed Consent

Some protocols may be determined to be HSR but still are potentially exempt from the Common Rule. 40 CFR 26, Section 26.101, lists multiple such scenarios. Exempt research in HSD most often falls into the following category.

“(4) Research , involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”

Even if an IRB determines that a study is exempt from the Common Rule, final approval by the Agency HSRRO is still required before the study can proceed.

Other HSR may qualify for a waiver of informed consent by the IRB for a variety of other reasons. In NHEERL, this is usually because the study presents no more than minimal risk to the study subjects. In these cases, the PI should follow the procedure outlined in the previous sections but request a waiver of informed consent from the IRB. If the IRB grants the request, the PI, in the cover memorandum to the Associate Laboratory Director, should include the reason for requesting the waiver from the IRB. Again, final approval by the Agency HSRRO is still required before the study can proceed.

5.5.3 Collaboration on Research Primarily Conducted Outside NHEERL

NHEERL investigators frequently collaborate on studies primarily being conducted at other institutions, such as other EPA laboratories, government agencies, and universities. Note that collaboration implies involvement as a Co-PI or Co-I, possession of personally identifying information, interaction with subjects, or involvement in other activities such as analyzing samples or interpreting data and drawing conclusions with the expectation of co-authorship of publications. Consultation, on the other hand, implies less direct involvement with a study, no interaction with subjects, no possession of personally identifying information, and generally does not result in recognition or co-authorship on publications. Further guidance on this issue can be found at the DHHS Office of Human Research Protections Web site, <http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm> . Collaboration, but not consultation, implies that the NHEERL investigator is engaged in HSR, and such participation requires NHEERL approval as previously outlined. The decision of whether an individual is a consultant or collaborator must be made by the HRPO Director.

5.5.4 Center for Environmental Medicine, Asthma, and Lung Biology

Consistent with the requirements of the Outside User Agreement to Provide EPA Research

Draft, April 2005

Facilities to the University of North Carolina at Chapel Hill, all research in the Human Studies Facility, regardless of funding source, must meet applicable EPA requirements. Research involving EPA staff, funding, special facilities or contractor support is subject to the standard EPA review process and written approval from the Division Director is required for the project to proceed.

Research involving human subjects without EPA involvement requires giving the Division Director copies of an IRB-approved protocol and informed consent form, and a copy of the approval from the funding organization. Upon receipt, there will be concurrent reviews by the Division Director, HRPO Director, and the Associate Director for Health. All reviews are to be completed within ten business days. At the end of this period or sooner, the Division Director will issue a written statement either approving or disapproving the study, or requesting further discussion.

5.5.5 Other Cooperative Agreements, Contracts and Interagency Agreements

Although relatively uncommon, research scenarios exist that do not fit into any of the above described categories. They vary substantially with regard to who is participating in the study, what their role entails, and where the actual research will be conducted. At a minimum, these studies should be discussed with the Division Director and the HRPO Director and will be handled on a case-by-case basis.

CHAPTER 6

HUMAN CONTROLLED-EXPOSURE STUDIES

Controlled-exposure studies involve the deliberate exposure of human subjects to pollutants under carefully controlled conditions. Exposure of humans to a given condition or stressor affords the unique opportunity to isolate, describe, and explain any health events associated with such an exposure. This type of research allows the identification of exposure – response relationships and can provide estimates of threshold exposures for humans. It may permit a better understanding of the specific nature and biological mechanisms that underlie the responses seen at low-dose exposures in the real world. Such work may also provide information about how the body absorbs, distributes, metabolizes, and eliminates a particular agent. Studies of this type provide critical information for more specific and targeted regulatory decisions and risk reduction or risk prevention strategies.

6.1 PURPOSE

This chapter describes the additional requirements governing the approval and conduct of controlled exposures of humans to pollutants (often called clinical studies or dosing studies at NHEERL) beyond those listed in the NHEERL Human Research Policy and those listed in Chapter 5 of this NHEERL Human Guidance document. Deliberate exposure by any modality is included in this definition and may include inhalation, ingestion, intravenous administration, dermal exposure or other methods. Some of the requirements in this chapter also apply to studies in which diagnostic or other test substances not normally considered to be pollutants are administered to human volunteers. Particularly applicable is the section describing procedures to assure and document the preparation and administration of the proper dose of any exposure substance.

6.2 STUDY JUSTIFICATION

Subjects deliberately exposed to pollutants may experience personal risk, without the individual benefitting from the gains that accrue to society as a whole from the research. It is thus imperative that the justification for conducting such research in humans be clearly presented and that the potential risks to the subjects be balanced against the potential benefits of the study. Many controlled human exposure studies entail minimal risk. As the risk to individuals increases, however, the potential benefit of the study to EPA and to society must be more compelling.

Controlled human exposure studies will not be initiated unless there are prior data from at least one of the following types of research.

- Toxicity testing in laboratory animals.

- Other human exposure research, such as epidemiologic studies or controlled human exposures.
- Studies of a very closely related chemical compound.

Such existing research must be used as follows.

- To help design the proposed study.
- To better understand and articulate the potential risks to study subjects.
- To clarify additional insights and benefits to be gained from the study.

Refer to Section 5.3.7 for specific issues that must be addressed in the Study Justification Document prior to approval of any human controlled-exposure research. Initial human controlled-exposure studies of a pollutant must be carried out on the least susceptible subjects and must be evaluated to assure that the responses of these least susceptible subjects conform to expectations prior to studies of more susceptible populations. Exposure doses in the initial controlled-exposure study should be similar to or lower than doses received by individuals in the environment or the workplace.

6.3 POLLUTANT SELECTION AND ADMINISTRATION CRITERIA

The pollutant in question must be present in the environment of interest or under consideration for introduction into that environment. Exceptions might include the use of well-characterized test substances for dosimetry or other types of studies. While such compounds may not necessarily be found in the environment, they may be related to those that are and may be safer to use.

Once a pollutant is selected for a study, a review of the relevant literature of the proposed pollutant must be undertaken. The review will include topics such as toxicology, epidemiology, structure – activity relationships, and exposure assessment. The goal is to identify and characterize the range of environmental exposures and to identify any risks that the pollutant may pose to humans. Additionally, the review will attempt to develop specific expectations of human response for the proposed study.

In most cases where research results may be used in the regulatory standard-setting process, the duration, rate of exposure, and conditions of exposure should be relevant to real-world exposure scenarios. Most controlled-exposure studies involve a single or a few acute exposures of short duration (usually a few hours). In some cases, including the following, it may be scientifically desirable to expose subjects to concentrations greater than what might be normally experienced in the environment.

- It may be more practical to deliver the total dose normally received in the environment over a 24-hour period during the course of a shorter controlled exposure (i.e. a higher concentration for a shorter duration).
- Identification of dose-response models that provide accurate and precise estimates for a variety of exposure conditions may require that response be measured at concentrations both below and above environmentally existing concentrations.
- Use of a pollutant with well-characterized effects (e.g. ozone) as a probe for understanding mechanisms of pollutant action or other aspects of human biology often requires the induction of effects of a certain magnitude that may require exposure to concentrations above what is normally present in the environment.

In all of these cases, the PI must provide convincing evidence that exposure to these higher concentrations is necessary to accomplish a desirable goal, that the health effects of the exposures are well known and very unlikely to be harmful to subjects, and that any risks that do exist are outweighed by the benefits of the study.

6.4 PROTOCOL PREPARATION

In addition to the steps listed in Chapter 5 for the preparation of all NHEERL human studies protocols, the following steps must be undertaken for controlled-exposure studies.

6.4.1 Initial Steps

For studies using on-site contractors for subject recruitment or engineering support, or requiring use of the Medical Station, the PI must obtain input from appropriate Project Officers and the Medical Station staff. In these cases, the study outline must contain sufficient detail so that these personnel can ascertain the roles they are being asked to play.

6.4.2 Medical Review

All human studies that involve controlled-exposure to pollutants must be reviewed by a physician. The review must address the following elements.

- Known risks inherent in the exposure and any procedures to be conducted have been identified in the protocol.
- Known risks specific to the proposed study population have been identified.
- Appropriate measures to reduce risk are in place.

- Appropriate medical criteria are in place for selection of the proposed study subjects.
- The investigative team and the medical staff are qualified to deal with any adverse medical events that could reasonably be anticipated to arise.

The physician reviewer must be identified as a reviewer on the NHEERL sign-off sheet. A physician-PI cannot review his or her own study. A physician Co-I, however, may provide the medical review.

6.4.3 Dose Calculation and Dosage Delivery Assurance

For any proposed experimental pollutant exposure, calculations must be presented that document the pollutant dose that a typical subject in the proposed study will receive during a nominal exposure to the desired target concentration. These experimental dose estimates must be compared to doses that an individual exposed in the environment would receive. If it is known or likely that some study subjects will receive doses which vary considerably from that of the typical subject in the proposed study (e.g. due to an inability to precisely control the exposure concentration, intersubject variation in the minute ventilation in an inhalation study, intersubject variation in rate of dermal uptake, etc.), this should be noted and discussed in the protocol and maximal allowable doses should be calculated that subjects may receive under the protocol. These calculations should be presented on a separate sheet entitled "Dosage Calculations" and included as part of the protocol package.

Most controlled-exposure studies in NHEERL take place in the Human Studies Division where pollutants are prepared and delivered by the on-site engineering support contractor, which follows rigorous QA/QC procedures to ensure accurate and reproducible delivery of pollutants to subjects. In some studies, however, the substance to be administered (e.g. pollutants, experimental medications, chemical compounds, dietary supplements, diagnostic materials, etc.) must be either prepared or administered by the PI or another team member. In these instances, the PI must develop a detailed Research Operating Procedure (ROP) that assures and documents that the substance is prepared properly and that the proper dose is administered..

In consultation with his or her Branch Chief, the PI will submit the ROP for review by an appropriate expert. The PI will incorporate suggested modifications, additions, and deletions into the final ROP. Whenever appropriate, experimental substances will be prepared and dispensed by a facility with experience and expertise in this area, such as the UNC Investigational Drug Pharmacy. The ROP must include specific plans for obtaining an independent verification of the stability, homogeneity, and concentration of the dosing agents prior to beginning a study; specific plans for obtaining further analyses of the dosing agents at specified intervals during the study; and specific acceptance criteria for these analyses. This requirement may be waived for substances

whose composition, purity, and stability are certified by the supplier such as over-the-counter vitamins or FDA-approved substances.

In some types of inhalation dosimetry studies, the preparation and/or administration of substances is not conducive to the use of either an on-site contractor or a facility such as an Investigational Drug Pharmacy. For these studies, the ROP must include specific plans for documenting the amount of material that is administered to the subject for each exposure. For other procedures such as methacholine challenge, the known purity and pre-packaged weight of the FDA-approved substance, as well as the incremental method of delivery, obviate the need for preparation by an Investigational Drug Pharmacy or additional analyses of the solutions to be administered. The ROP in these cases, however, must explicitly describe the process for preparation and delivery of the substance as well as documentation that the procedures were followed for each test. No study will be allowed to begin until the Dosing Review Officer and PI's Branch Chief indicate that the ROP provides assurance and documentation that the test substance will be prepared and administered properly.

These requirements do not apply to the use of over-the-counter and prescription medications that are listed in the Medical Station's Standing Physician Orders. They also do not restrict the use of medications not part of the study protocol that are prepared, administered, and/or prescribed to study subjects for health reasons or for clinical procedures performed by licensed medical staff involved in the studies. This policy does apply, however, to study protocols that use drugs, compounds, and supplements in a manner that deviates from their FDA-approved use, such as varying the route, interval, or method of administration, or changing the dosage.

6.5 FINE-TUNING OF PROTOCOL IMPLEMENTATION

After final approval by the Agency HSRRO, the study investigators must ensure that all parties, including investigators, nurses, recruiters, engineers, and physicians have any remaining questions answered and that the logistics of the study are reviewed satisfactorily before any subjects are actually studied. A dry run covering everything except pollutant exposure and the performance of invasive procedures is strongly encouraged to test the proposed protocol.

CHAPTER 7

EPIDEMIOLOGICAL STUDIES

Epidemiology involves the study of the distribution and determinants of health-related states or events in specified populations and the potential application of this study to the control of health problems. This chapter applies to the traditional epidemiological study in which the association between an exposure of interest and a health outcome of interest is estimated, as well as to other study types including exposure assessment, biomarker investigations, and methods development for eventual use in epidemiological studies. These studies usually involve the collection and study of data or samples (including biological samples) from individuals or populations or from an environment linked to individuals or populations. For the purposes of this document, studies in which individuals are deliberately exposed to a pollutant are not considered to be epidemiological studies and are discussed in Chapter 6.

7.1 PURPOSE

This chapter describes the additional requirements governing the approval and conduct of epidemiological studies beyond those listed in the NHEERL Human Research Policy and beyond those listed in Chapter 5 of the NHEERL Human Research Guidance document.

7.2 INDIVIDUAL SUBJECTS

Multiple factors need to be considered regarding the rights and privacy of study subjects. Investigators should maintain a high level of awareness about how any aspect of the study may burden the subject or compromise the confidentiality of a subject's personal identifying information.

7.2.1 Subject Burden

The expected subject burden must be considered and described in the protocol. Subject burden includes not only the time and effort needed to complete the study (transportation to the study site, appointments available only during certain hours, questionnaires to be mailed back, etc.) but also exercise tests, medical examinations (including venipuncture), and even the psychological stresses of participation.

7.2.2 Personal Environment Sample Collection

Protection of the subject's personal property and quality of life is especially important when collecting environmental samples (house dust, personal wipes, water samples, etc.) from a

subject's home or work area. Methods used to collect, transport, store, analyze, and dispose of personal environmental samples must always protect the confidentiality of the subject and the subject's personal environment.

7.2.3 Spatial and Geographical Information Systems (GIS) Data

Spatial and GIS data can be very useful in examining patterns of exposures and/or outcomes in a given geographical area. Such data, however, must be carefully used with respect to storage and reporting results. In addition to normal procedures for assuring confidentiality of samples and data, spatial and GIS data require additional precautions in handling. By definition, spatial and GIS data are considered "identifiers." Thus, whenever these data occur in a database, they must be password-protected if stored on a local or network drive. Spatial and GIS data on discs (CD-ROM, floppy, zip, etc.), tapes, and printouts must be stored in a locked facility, such as a locked filing cabinet or storage room.

Spatial and GIS data must be reported as aggregate data so that no one individual within the data set can be identified from either spatial results or GIS mapping. Spatial or GIS mapping must not be used in reporting if data are collected in a sparsely populated area, such as a rural community or a small town, or if there is a rare outcome or exposure with the potential to identify a specific individual.

7.3 COMMUNITY-BASED OBSERVATIONAL STUDIES

In certain instances, such as collecting drinking water or outdoor air samples, personal environment collection may have implications not only for the individual from whom collection is obtained but also for a community as a whole. In these cases, consideration of community notification and/or participation is necessary. Formation of community advisory boards may also be necessary. The protocol must state whether the community as a whole should be informed of the research before it will be conducted and of the results after the study is completed; how the community will be notified, if necessary; and whether community advisory boards will be formed.

Additional procedures are needed for conducting community-based observational studies. Ethical considerations are required both for the individual subjects in the study and for the community as a whole. In addition to items listed in Section 5.3.7, the following communication procedures are part of the planning process and the results of these deliberations must be included in the Study Justification Document.

- A communications plan should be developed to inform the local, state, and the appropriate regional EPA Office of the proposed study. The Fact Sheet developed for the EPA Protocol Package can be used as part of this process.
- If requested, the PI should be prepared to offer a pre-study briefing to local, state, or

Draft, April 2005

EPA regional officials. The Branch Chief, Division Director, and appropriate Associate Director must be informed of the planned briefing.

- Investigators should seek the advice of local and state officials on the advisability of a community advisory panel and other forms of community outreach, such as meetings to explain the study and its possible implications to the community as a whole.
- Individual results are reported to the subjects as outlined in the informed consent form.
- The investigator must describe if and how results will be provided to a community prior to publication or other public release of information. If a public meeting is planned, the PI must inform the Branch Chief, Division Director, and the Associate Director for Health or Ecology of the planned date and give a brief synopsis of the results to be presented. Depending on the classification and/or level of visibility of the study, other clearance processes may also be required.

CHAPTER 8

STUDY OF DATA AND HUMAN TISSUES, INCLUDING IN VITRO RESEARCH

8.1 PURPOSE

This chapter describes the principles and guidelines governing the conduct of research on data, human tissues, and in vitro studies in NHEERL.

Before beginning an investigation using either data or tissue from another study involving human subjects, the researcher must consult the HRPO Director to determine whether the proposed research is subject to the Common Rule. The rules governing that decision are very complex. Some studies will be considered HSR and therefore are subject to the Common Rule and require a complete NHEERL Protocol Package. Other studies may be similar except for a slight nuance and considered "not HSR" and therefore not subject to the Common Rule and not requiring a standard NHEERL protocol package. NHEERL researchers must also understand that even though an IRB has decided that a particular study is exempt from its further review, only the Agency HSRRO can decide that the study is exempt from further EPA review.

8.2 DEFINITIONS

Because HSR refers to research involving living human beings, the following definitions are important.

- **Human Tissue**— Any cells, cell lines, fluids, or other biological tissues originally collected from a **living** person.
- **Cadaver**— A **deceased** person or portion thereof, including, blood, fluid, arteries, or any other tissues.

The Common Rule does not apply to use of tissue from a cadaver. The Common Rule does apply, however, if samples were removed for research purposes while the individual was still alive.

8.3 CADAVER USAGE

Although not covered by the Common Rule, the use of cadavers is subject to the laws of states, localities, and foreign governments. Like any other study involving tissue of human origin, studies involving the use of tissue or samples from cadavers must be discussed with the HRPO Director.

In rare circumstances, a protocol package may need to be prepared and should include the following items in addition to those listed in Chapter 5.

- Copies of relevant laws on procurement, treatment, and disposition cadavers. The Uniform Anatomical Gift Act has been adopted in some form in all states and the District of Columbia.
- Documentation indicating that cadavers will be properly and legally procured; that vendors will be informed of the intended use of the cadavers; and that cadavers will be used in a manner consistent with the intent of the donor. Any restrictions by the donor must be honored in the protocol.
- A statement that the privacy of the donors will be maintained in use of tissue from cadavers.
- Description of procedures for the treatment, storage, and disposal of the cadavers. These procedures must ensure ethical treatment of the cadavers and must comply with the wishes of the donor or the next-of-kin.

8.4 GENETIC STUDIES

As with many types of biological research, the possibility of identifying individuals with a disease susceptibility may occur, especially in studies that correlate genetic changes or biomarkers with susceptibility to specific diseases. Such studies must have the most stringent safeguards for subject privacy and confidentiality. Most IRBs have specific requirements for the use of human material in genetic studies, especially with respect to informed consent. The PI in such a study should first consult the HRPO Director, and, if necessary, an IRB representative to determine the necessary requirements before developing the full protocol package. Confidentiality and release of study results are particularly important in these cases.

8.5 STORED SPECIMENS

There are several categories of stored specimens collected in HSR, including specimens to be stored for previously stipulated tests; for as-yet-undesignated tests, but excluding genetic studies; for as-yet-undesignated tests that may include genetic studies, with personal identifiers accompanying the specimen; and for as-yet-undesignated tests that may include genetic studies, but with no associated personal identifiers. Each category has specific requirements for protection of the research subject.

8.6 SPECIMENS OBTAINED FROM OTHER RESEARCHERS OR COMMERCIAL TISSUE BANKS

Multiple opportunities exist for researchers to obtain specimens of human origin from other colleagues or from commercial tissue banks. A guiding principle is that the PI and Division Director should only use specimens that were obtained in an ethical manner and, when applicable, the specimen provider can provide proof of IRB approval of the protocol being used to procure, store and distribute the specimens. The HRPO Director must be notified before any research is initiated involving human specimens of any sort.

CHAPTER 9

NHEERL EMPLOYEES AS RESEARCH SUBJECTS

Because the protection of all human research subjects is an extremely high priority at NHEERL, that same priority must naturally extend to NHEERL employees who experiment on themselves, participate in NHEERL human studies, or request co-workers to take part in these studies.

9.1 PURPOSE

This chapter describes additional requirements governing the participation of NHEERL employees as subjects in human research activities conducted in NHEERL beyond those listed in the NHEERL Human Research Policy and in Chapter 5 of this NHEERL Human Research Guidance document.

EPA conducts an extensive health monitoring program on its employees. This Occupational Medical Surveillance Program (OMSP) is not considered research because its aim is not to create "generalizable knowledge" as defined by the Common Rule. Therefore OMSP is not covered by the Common Rule or in this document.

9.2 GENERAL GUIDELINES

For any research activity in which an NHEERL employee will participate as a subject, including donating biological specimens for methods development, the following guidelines must be followed.

- Employees are very strongly discouraged from conducting research on themselves. Alternatives to using employees include obtaining subjects identified through an appropriate recruitment mechanism or procuring anonymous specimens from internal or external specimen banks. The HRPO can advise investigators on how to obtain suitable subjects or specimens.
- There must be no direct or indirect coercion of employees to participate as subjects in NHEERL research activities. Supervisors are not allowed to ask employees they supervise to participate as subjects in NHEERL research studies. If employees do choose to participate, they are subject to the same precautions as any other research subject to protect the confidentiality of their data.

9.3 REQUIREMENTS FOR PARTICIPATION AS A HUMAN SUBJECT

For any research activity meeting the definition of HSR in either the Common Rule or EPA Order 1000.17A, Change A1, NHEERL employees participating as subjects are also subject to the following additional requirements.

- No employee may participate as a subject in HSR that circumvents oversight by an IRB or by Agency review and approval procedures.
- All employees must go through the same screening process required for non-employee subjects, including identical inclusion and exclusion criteria for participation.
- The study protocol must contain a statement of the expected number and duration of time periods that subjects, including employees, will be expected to spend in the study. A copy of this statement must be provided to the employee. The consent form must appropriately cover additional liability issues, if any, that are generated by employee participation either on his or her own time or on government time.
- An employee who feels that his or her rights have been breached or to whom an injury has occurred should contact the Division Human Research Officer, the HRPO Director, and/or the Chairman of the IRB at the telephone numbers listed in the consent form.

9.4 NON-RESEARCH ACTIVITIES

Some activities involving human subjects are not HSR because they do not meet the definition of **research**. Such studies are not subject to the Common Rule and do not require approval by the Agency HSRRO. The decision as to whether a human research activity meets the definition of HSR must not be made by the PI, but by the HRPO Director, with input, if necessary, from the appropriate IRB.

For some procedures that involve very low risk of personal injury and low risk of ethical mistreatment, an NHEERL PI may be granted permission to participate as a subject or to include other NHEERL employees as subjects. To obtain this permission, the PI must write a memorandum describing the activities and the risks, and why this activity does not meet the definition of HSR. The memorandum must be sent through the Branch Chief to the HRPO Director and must be approved by both before the study can begin.

The following collection procedures may fall into this category. The HRPO Director may make additions or deletions as needed.

9.4.1 Biological Samples

- Breast milk samples
- Breath collection
- Buccal specimens
- Dermal wipes
- Fecal specimens
- Hair specimens
- Nail specimens
- Nasal lavage
- Spontaneously generated sputum
- Saliva collection
- Urine specimens

Note that several common types of samples, including venous blood samples, are not included. Venipuncture is more invasive and can have more significant consequences than the other listed procedures. Many individuals become light-headed or faint when having blood drawn, or can be made anemic with excessive blood drawing. Semen samples are not included because of issues concerning privacy and embarrassment surrounding the collection process. Neither genetic analyses nor other analyses that may yield sensitive or potentially unfavorable information may be performed on any samples collected under this category unless the samples are pooled or are otherwise completely anonymous, with no means of determining the identity of the donors.

9.4.2 Other Procedures

- Routine pulmonary function (spirometry and body plethysmography)
- Blood pressure
- Pulse oximetry
- Heart rate variability

9.4.3 Survey Questionnaires

For questionnaire completion by employees to be allowed, the following conditions must be met.

- When employees take questionnaires to evaluate the questions and/or the time needed for completion, individual answers to questions cannot be entered and stored in a data base. Only evaluative information, such as suggested changes in wording, format, or that it took 30 minutes to complete, can be collected.
- Answers to individual questions from questionnaires may be entered and stored in a data base if, and only if, the questionnaires are completely anonymous and the identity of the employees cannot be determined by other means.

APPENDIX A

NHEERL HUMAN RESEARCH SIGN-OFF SHEET

PI (Name/Division):

PROTOCOL TITLE:

NAME OF APPROVING IRB:

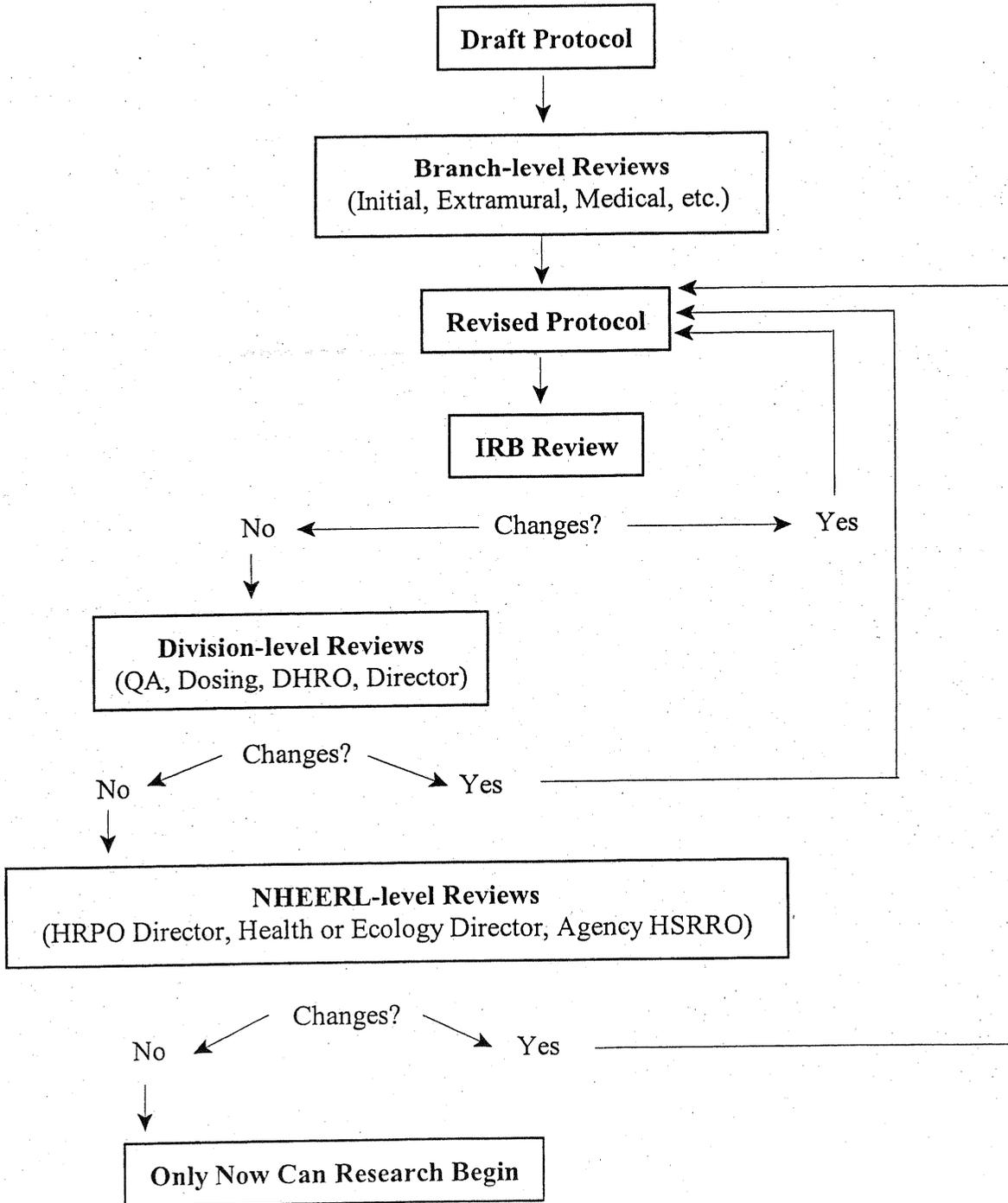
IRB-ASSIGNED PROTOCOL NUMBER:

REVIEWS (Attach to EPA Protocol Package)		
Reviewer	Name	Date
Peer Reviewer1		
Peer Reviewer2		
Statistician		
Physician		
APPROVALS		
Official	Signature	Date
Division Human Research Officer		
Branch Chief		
IRB	<i>(Attach signed approval letter)</i>	
Dosing Review Officer		
Division Quality Assurance Officer		
Division Director		
HRPO Director		
Associate Director for Health or Ecology		
Agency Human Subjects Research Review Official		

effective 2/28/2005

APPENDIX B

FLOW DIAGRAM OF REVIEW PROCESS



HUMAN RESEARCH POLICY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS RESEARCH
LABORATORY
(9-27-04)

1. PURPOSE

This document presents the EPA National Health and Environmental Effects Research Laboratory (NHEERL) policy on the general requirements and responsibilities for initial approval, conduct, and oversight of human research activities conducted, or supported, by NHEERL. This policy covers research activities that involve the collection or study of data or samples that are of human origin or are otherwise linked to human data. This includes both the collection of information or measurements from, or about, humans and the analysis of existing data sets, tissues, or other specimens of human origin. Additional guidance for specific situations and study types is available in an accompanying NHEERL Human Research Guidance document. The Guidance document provides guidelines for approval and conduct of HSR in general, as well as for controlled human exposure studies, epidemiology studies, human tissue studies, and studies using NHEERL employees as subjects.

2. APPLICABILITY

This policy applies to all research activities:

- a. Conducted by or supported by NHEERL or in which NHEERL employees collaborate with other institutions, and
- b. Meeting the definition of research involving human subjects as defined by the Common Rule (40 CFR 26.102) and given below.

3. DEFINITIONS

All definitions listed in EPA Order 1000.17, Change A1 and in the Common Rule (40 CFR 26.102) [both documents found at http://intranet.epa.gov/rmpolicy/ads/orders/1000_17a.pdf] apply to this policy. Four key definitions derived or summarized from these documents are listed below.

- a. *Human subject* [40 CFR 26.102(f)] and [EPA Order 1000.17, Change A1, 3(d)] means a living individual about whom an investigator conducting research obtains
 - (1) Data through intervention or interaction with the individual, or
 - (2) Identifiable private information.
- b. *Research* [40 CFR 26.102(d)] and [EPA Order 1000.17, Change A1, 3(a)] means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this

policy, whether or not they are conducted or supported under a program which is considered research for other purposes.

- c. *Human subjects research (HSR) or Research involving human subjects.* Research activity that meets the definitions of both research and human subject given above and in 40 CFR 26.102 and EPA Order 1000.17, Change A1.
- d. *Exempt research* [EPA Order 1000.17, Change A1, 3(b)]. Human subjects research falling into one of several categories described in 40 CFR 26.101 (b), which is exempt from the Common Rule.

4. POLICY

- a. All research activities meeting the definition of human subjects research (HSR) conducted or supported by NHEERL shall comply with EPA Order 1000.17, Change A1, with the Common Rule (40 CFR 26), and with this policy. In addition, research involving pregnant women, fetuses, and neonates; prisoners; and children shall comply with Subparts B, C, and D, respectively, of the Common Rule, as codified by the Department of Health and Human Services in 45 CFR 46 [<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>].
- b. All research activities that collect or use data or materials of human origin must be classified as either meeting, or not meeting, the definition of HSR by the Director of the NHEERL Human Research Protocol Office (HRPO) prior to the initiation of any research.
- c. All HSR must be approved by the NHEERL Associate Director for Health or Ecology prior to submission to the Agency Human Subjects Research Review Official (HSRRO).
- d. All HSR must be either approved or determined to be Exempt Research by the Agency HSRRO before any research is conducted by or supported by NHEERL.
- e. The NHEERL HRPO is the official NHEERL repository for protocol packages (see Section 5) involving human research activities. Complete copies of the original protocol package, amendments, Institutional Review Board (IRB) approval letters, consent forms, renewal application packages, adverse event reports, and all correspondence to and from the IRB must be provided by the Principal Investigator to the HRPO prior to the conduct of (additional) research.
- f. Each NHEERL Division conducting HSR shall appoint a Division Human Research Officer (DHRO) who serves as the key Division resource for day-to-day compliance with existing Federal regulations and with this NHEERL human

research policy.

- g. Any violation or deviation of the conduct of research from an approved HSR protocol or any occurrence of an adverse event, including subject injury or unexpected response, must be immediately reported by the Principal Investigator to the IRB, to the Director of the NHEERL HRPO, and to NHEERL management, which will report the information up the NHEERL chain of command, and, if indicated, to the Agency HSRRO.
- h. Each NHEERL employee engaged in the conduct of HSR, or in the HSR approval chain, shall complete, each calendar year, at least one hour of relevant training that must be approved by the Director of the NHEERL HRPO. Documentation of all such training shall be provided to the Director of the NHEERL HRPO. Each employee engaged in a human subjects research protocol must also meet any training requirements of the IRB overseeing the specific protocol.

5. GENERAL REQUIREMENTS

To obtain approval for an HSR study from the appropriate NHEERL Associate Director (AD), a human subjects research protocol package must be prepared that includes the elements shown below. Further guidance on the preparation of this package and the required reviews is found in the accompanying NHEERL Human Research Guidance document.

- a. NHEERL documents
 - (1) Cover letter
 - (2) Sign-off sheet
 - (3) Fact Sheet
 - (4) Study Justification Document
- b. IRB package
 - (1) IRB approval letter
 - (2) Written research protocol
 - (3) Consent forms approved and stamped by the IRB
 - (4) Questionnaires and advertising approved and stamped by the IRB
 - (5) HSR training certificates
- c. Reviews
 - (1) Any required extramural scientific reviews with written responses
 - (2) Any required medical, statistical, or other reviews with written responses

6. RESPONSIBILITIES

The following NHEERL organizational and individual responsibilities apply to the development, management, and conduct of any research study involving human subjects.

a. Principal Investigator (PI)

The PI is responsible for all aspects of the study and must be exceedingly knowledgeable about HSR regulations, the science supporting the proposed study, and any potential risks to subjects. The PI has specific responsibilities to the EPA, to the IRB, and to the subjects participating in the research. The PI must:

- (1) Understand and comply with EPA and NHEERL human research policy.
- (2) Understand and comply with the requirements of all IRBs with jurisdiction over a particular study.
- (3) Prepare a protocol package that clearly and accurately presents the scientific rationale for the study, the potential risks to the subjects, and the expected benefits of the study so that scientific and ethical reviewers have all the necessary information to make objective judgements about the protocol.
- (4) Ensure that the initial review and approval of the study by EPA is completed.
- (5) Minimize risk and ensure the safety and well-being of the subjects.
- (6) Conduct the study in an ethical manner.
- (7) Maintain accurate records, including documentation of informed consent and current IRB approval, and send copies of all correspondence with the IRB of record, including all protocol amendments and renewals, to the NHEERL HRPO.
- (8) Report any adverse effects or noncompliance with the protocol to the NHEERL HRPO Director, NHEERL line management, and to the IRB.
- (9) Oversee study staff.

b. Branch Chief (BC)

The PI's Branch Chief is responsible for ensuring that the composition of the research team is appropriate; that all requirements for initial reviews, meetings, and written responses have been met; and that the written protocol is scientifically and ethically sound. In particular the BC must:

- (1) Ensure that the PI or a Co-PI has significant previous HSR experience.
- (2) Ensure that the research team has appropriate scientific and medical expertise to safely and ethically realize the goals of the study.
- (3) Ensure that required meetings among the PI and all relevant parties (e.g. medical staff, recruitment staff, etc.) occur prior to protocol preparation and again prior to study commencement.
- (4) Ensure that all required written reviews (e.g. medical review, statistical review, extramural peer review, etc.) have been completed and that the PI

- has adequately addressed the reviewers comments in writing.
- (5) Review the protocol and consent form to ensure that the proposed study is scientifically sound and clearly presented, and that he/she is satisfied that the risks to subjects have been accurately presented in both the protocol and the consent form.

c. Division Human Research Officer (DHRO)

The DHRO will review the proposed protocol and consent form and must:

- (1) Ensure that they are consistent with the requirements of both the EPA and the IRB and that EPA-required language has been included in the consent form.
- (2) Ensure that the protocol identifies the risks to subjects and the measures to reduce this risk.
- (3) Ensure that ethical issues which should be clarified or addressed prior to submission to the IRB are identified.

d. Division Director (DD)

The DD will ensure that all lower-level reviews have been completed and that the BC, DHRO, and other Division reviewers are aware of, and are fulfilling, their HSR review responsibilities.

e. Director, NHEERL Human Research Protocol Office (HRPO)

The Director of NHEERL HRPO is responsible for initial review of the protocol package and maintenance of NHEERL records for HSR. The Director will

- (1) Ensure that the protocol package contains all necessary elements for approval by the appropriate Associate Laboratory Director and the Agency HSRRO.
- (2) Ensure that all required reviews have been completed and adequately addressed by the PI.
- (3) Ensure that the protocol identifies the risks to subjects, the measures taken to reduce this risk, and any ethical issues that must be further addressed by the PI.
- (4) Ensure that the consent form contains any specific language required by NHEERL.
- (5) Maintain all HSR records, including the original protocol package and approval letters, subsequent amendments and renewals with IRB approval letters, and any other correspondence with the IRB.

f. NHEERL Associate Director (AD) for Health or Ecology

The appropriate NHEERL AD provides the final NHEERL review prior to Agency review. Specific responsibilities include:

- (1) Review of the protocol package to ensure clarity of information.
- (2) Review of the package for any scientific, policy, or ethics issues that need

- to be further clarified.
- (3) Transmission of the approved protocol package to the Agency HSRRO.

g. All NHEERL employees

All NHEERL employees are responsible for reporting the following to the NHEERL HRPO and the appropriate DD:

- (1) Any serious or unanticipated harm experienced by research subjects.
- (2) Any deviations of HSR from the approved protocol.
- (3) Any unethical or unsafe behavior by anyone associated with HSR conducted in or supported by NHEERL.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL CENTER FOR ENVIRONMENTAL RESEARCH
WASHINGTON, DC 20460

SEP 23 2002

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Decision on Suspension of Human Clinical Studies at NHEERL

FROM: Peter W. Preuss *Peter W. Preuss*
EPA Human Subjects Research Review Official

TO: Lawrence W. Reiter, Director
NHEERL

I am today lifting the indefinite suspension I imposed on human clinical research at NHEERL. My decision is based upon the follow up activities and actions taken by NHEERL subsequent to your informing my office on July 22, 2002, that a protocol violation had been identified at the Human Studies Division (HSD). At that time, you indefinitely suspended EPA's clinical research activities at the Human Studies Facility (HSF). In my role as the EPA Human Subjects Research Review Official, I directed that the suspension of human clinical studies at NHEERL continue indefinitely to allow for an independent third-party review of the protocol violations to be conducted - including the development of recommendations for strengthening the guidelines and safeguards to be followed in the conduct of human clinical research. On August 19-21, 2002, an independent review panel met at the HSF and reviewed information on the policies and practices related to human clinical studies and the documentation of the protocol violations that had occurred in the last year at HSD. The panel provided a number of recommendations in their report to me dated August 21, 2002. You and your staff, in turn, evaluated your clinical research practices and the recommendations of the review panel, and developed a corrective action plan that was completed on September 5, 2002. I have reviewed this corrective action plan and find it to be satisfactory. In lifting the suspension, I am confident that NHEERL is committed to full implementation of the actions outlined in the plan.

cc: Paul Gilman
William Farland
Henry Longest II
Hal Zenick
John Vandenberg

Attachment (4)

FAX TRANSMISSION

OFFICE OF RESEARCH & DEVELOPMENT

1300 PENNSYLVANIA AVE., NW

WASHINGTON, DC 20004

202/564-6825

FAX: 202/565-2444

To: L.Reiter,H.Zenick, J. Vandenberg Date: 9/23/02

Fax #: Pages: 2 , including this cover sheet.

From: Peter W. Preuss

Subject:

August 15, 2003

Human Studies Division's Implementation of the Corrective Action Plan

Reporting Incidents and Responsiveness

ORD needs to develop a well-defined, streamlined process for when and to whom non-compliance should be reported.

- Elston Seal and Roger Cortesi have developed such a plan in December 2002, with minor modifications in April 2003. Both Roger and the NHEERL Protocol Office have the plan. The plan has not been widely distributed to investigators because their only part in it is to notify HSD management and the IRB of any protocol deviation. At that point, other EPA staff members will take over with the reporting process. Nevertheless, the plan is being posted to a web site accessible by all HSD employees. In addition, the web site will contain other useful information relevant to human studies.

A process is needed for timely, efficient action relative to the protection of human subjects (in the event of non-compliance).

- We will continue to first locate people from the information given to us in their study charts, followed by using the subject recruitment contractor. A requirement for timely location of "lost" research subjects is part of the new subject recruitment SOW. The new contract will be issued in mid-October, 2003.

A streamlined process is needed to facilitate notification of subjects.

- In October, 2002, the NHEERL Ethics Official (currently the HSD ethics official) has identified the key steps needed to accomplish this. The NHEERL Ethics Official will work with the IRB of record and the primary investigator to ensure that all appropriate steps are taken.

Assuring Dose Delivered to Subjects

NHEERL must assure with absolute certainty the dose delivered to subjects, including independent verification of stability, homogeneity, and concentrations of dosing solutions prior to subject exposure.

- This policy is directed toward non-TRC exposures; the TRC exposure monitoring system is state of the art and is being sustained. For the non-TRC exposures, a policy was initiated but it has not been applied yet because no studies using non-TRC dosing have been carried out by the Human Studies Division since the

summer of 2002. Upon first application, the UNC pharmacy, under contract, will provide independent verification of concentrations of dosing solutions for environmental agents employed in non-TRC clinical studies at the time of dosing.

Identify (by the investigator) an acceptable range for the delivered dose (or dosing solutions) for each protocol to indicate more precisely when an incorrect dosing event has occurred.

- All current protocols underwent review in 2002 and as current studies are renewed and new studies are developed an evaluation of acceptable dosing range occurs for all studies involving deliberate dosing of subjects. The investigator identifies the acceptable dosing range and this is reviewed by the branch chief early in the protocol development process and reviewed again by the division director and NHEERL Human Studies Research Review Official upon protocol approval.

Measures of delivered dose should be included in all active protocols, whether or not delivered dose is the parameter of concern.

- This has been done for all current protocols.

Periodic re-review and audit of clinical studies to proactively identify and correct any problems, as well as improve study protocols.

- Different venues for conducting this periodic review are being evaluated before a standardized or recommended venue is set as divisional policy. This is an aspect of the new Protocol Office responsibilities that Dr. Seal is addressing now, with the advent of the Protocol Office (see below). This will be developed fully after work on the Laboratory Human Research Policy and Guidance Document is finished.

Institutional Review Board Interactions including Subject Consent Process

Consider establishment of a centralized Protocol Office.

- A centralized Protocol Office has been established in HSD. One of the main reasons Dr. Elston Seal chose not to retire at the end of April 2003 was because he wanted to get the Protocol Office established and could do it with the help of Monica Nees, a SEEP employee, who joined the HSD staff early in 2003. The Protocol Office is undertaking a very active role in review and creation of NHEERL and HSD human studies policies, in tracking current and new protocols, in evaluating procedures and identifying opportunities for promoting the culture of subject safety throughout the Laboratory including through special seminars, auditing procedures, support of mentoring programs, etc. This is a significant

change to division programs.

Make EPA scientific review comments available to the IRB.

- Protocols requiring scientific review are now required to obtain review before submission of the protocol package to the IRB. HSD implemented this policy in October 2002.

Use a consent auditor to identify ways in which the consent process can be improved.

- [REDACTED]

Simplify consent form language.

- This is an ongoing project that requires negotiation with the IRB. Given the multitude of IRB's that HSD studies are reviewed by, the implementation of this recommendation will be unique for each study protocol. However, changes in the area will largely be driven by the IRBs involved and what language they want to see in the protocols.

Add subject's initial blank at the bottom of each consent form page.

- This has been a requirement for all new consent forms since October 2002 and for all renewed consent forms from the time of renewal.

Add more complete investigator and subject certification statements.

- Language will be incorporated into each consent form describing the certification requirements that have to be met.

Consent forms should list all investigators and their phone numbers and a 24-hour contact number.

- All investigators are listed on consent forms, however only the phone numbers of the Principal Investigators are listed in the consent forms. There is no real necessity to list the phone numbers of all of the investigators, such as technicians.
- A 24-hour contact system has been implemented for clinical studies. The Epidemiology and Biomarkers Branch maintains a toll-free number to facilitate contact with subjects in field studies.

Designated Institutional Official should be provided with copies of all pertinent IRB meeting minutes.

- Dr. Seal now receives the minutes of all four UNC Medical School IRBs. In nearly all minutes there is nothing that pertains to HSD.

Training, Mentoring, and Development of a Culture of Safety

Use of simulations or dry-run exercises with appropriate levels of physical or psychological fidelity as a technique for training and assessing new quality control processes or rapid-pressured decision-making responses to potential subject complications.

- Beginning in January 2003, simulations or dry runs are a required part of all on site protocols. Field studies conduct extensive training of field staff (EPA and contractors) and then run a minimal number of subjects to assure proper procedures as designed can be implemented.

HSD should establish a safety culture to ensure that a concern for safety is actively maintained on an ongoing basis. Bring in safety experts as speakers or seminar leaders from related disciplines, institute a speaker series.

- This change in culture was launched in December 2002 with the invitation of Dr. Kerm Henricksen. He gave a seminar entitled: "New Directions in System Safety," and conducted a series of listening sessions where a variety of concerns and issues were raised and discussed. [REDACTED]

- [REDACTED]

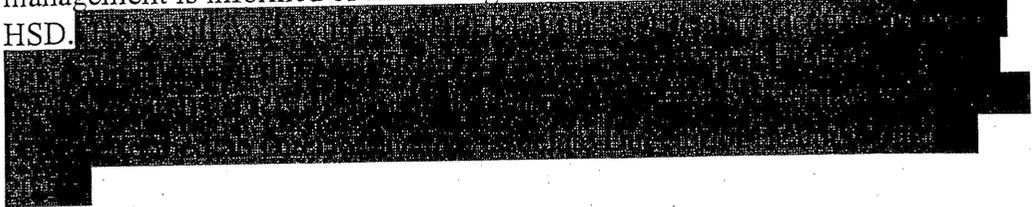
Conduct brainstorming sessions focused on areas of vulnerability.

- This has occurred with internal meetings to brainstorm about issues, such as subject safety. In addition, an internal committee drafted a document outlining a variety of suggestions for training and "Grand Round" types of seminars that could be conducted on a regular basis. [REDACTED]

[REDACTED]

Identify means of training of upper management to gain exposure to new concepts and principles of safety.

- Upper management have been informed of changes in policies and procedures. New issues, as they arise, are communicated to upper management. Upper management is informed of all training and seminar opportunities organized by HSD.



Institute specific training related to technical and equipment-related study aspects.

- The field studies have a requirement for annual training. With the recent purchases of new equipment, training sessions have been designed to orient new members of HSD to their use.

Create check lists of required screening procedures and activities, including signed consent form.

- Check lists exist for many subject related activities, including signed consent forms. HSD will add examples to the Human Subjects section of the HSD intranet web site.

Develop and implement a comprehensive mentoring program.

- Starting in September 2002, branch chiefs hold regular meetings with post docs. The HSD division director will meet a minimum of once a year with postdocs. PIs are urged to consider additional ways to improve mentoring of their post docs and students. On an annual basis this will be discussed among PIs and best practices will be the focus of the discussion.

Richard Hermann, MD, MPH
National Health and Environmental
Effects Research Laboratory
U.S. Environmental Protection Agency

Part 1

Background and Basics of Human Subject Research

RESEARCH & DEVELOPMENT

Building a scientific foundation

sound environmental decisions

What is Human Subjects Research?

- **Research** means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to **generalizable knowledge**.
- A Human **subject** means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

Types of Human Subjects Research

- - Epidemiological studies
 - Surveys
 - Studies involving intentional exposures, such as:
 - Exposure and biomonitoring studies
 - Metabolism
 - Clinical trials
 - Repellent efficacy tests

Value of Human Research

- Human subjects research has been central to many medical and public health advances
- Human subjects research has been central at the EPA for a number of key standards and regulations, for example:
 - Ozone
 - Particulate matter

Historical Background

- Nuremberg Code (1947)
 - *“The experiment should be such as to yield **fruitful results** for the good of society, unprocurable by other methods or means of study, and **not random or unnecessary in nature.**”*
- Declaration of Helsinki (1964)
 - World Medical Assembly
 - *“The primary purpose of medical research involving human subjects is to **improve...the understanding of the etiology and pathogenesis of disease.**”*

Historical Background (cont)

- **The Belmont Report (1979)**
 - Cornerstone of U.S. human subjects ethics documents
 - *Principles: respect for persons, beneficence and justice.*
- **The Common Rule (1991)**
 - A rule promulgated by 18 Agencies jointly that describes what may and may not be done, and the principles and practices that must be followed **when the United States government (USG) is conducting or supporting human subjects research.**

The Common Rule

- Requirements for approval by an Institutional Review Board (IRB), and informed consent requirements.
- Many private U.S. institutions adopt Common Rule standards for human subjects research.
- The Common Rule duty of EPA is to get certification that the research has received appropriate ethical review.

Historical Background (cont)

- DHHS 45 CFR 46 (2001)
 - Codified and revised the Common Rule to elaborate on special protections for vulnerable populations:
 - Subpart B - pregnant women, fetuses, and neonates
 - Subpart C - prisoners
 - Subpart D - children

EPA Order 1000.17, Change A1

(July 1999):

- *Policies and Procedures for the Protection of Human Subjects in Research Conducted or Supported by EPA.*
 - Internal administration of the Common Rule
 - Establishes a Human Subjects Research Review Official (HSRRO) to assure that all EPA conducted or supported research using human subjects complies with the Common Rule
 - Provides provisions for foreign studies

EPA Roles with Human Subject Research Data

- EPA performs or funds human subjects research:
 - Studies in ORD Laboratories and Centers
 - Extramural funding through ORD STAR grants
 - Program Offices and Regions
 - **All must comply with the Common Rule**
(and de facto DHHS 45 CFR 46) and EPA Order 1000.17,
Change A1
- EPA also retrieves and uses data generated by external research (“third party”). These parties are not necessarily subject to the Common Rule.

EPA Reviews under the Common Rule

- - On occasion, EPA has decided that the IRB has overlooked possible risks to subjects. When this has happened, discussions have resolved the issue.
 - On occasion, we have requested changes in the consent document.
 - Over the past six years, EPA has averaged about fifty projects per year requiring decisions from the HSRRO.
 - Of these, a small number have been human controlled-exposure studies.

NHEERL Human Research Policy

- Provides guidance to NHEERL investigators and managers on the ethical conduct, review, and approval of all human research activities.
- Ensures the safety and rights of human research subjects
- Manner consistent with the Common Rule (40 CFR 26), EPA and NHEERL policy
- Details the responsibilities for Principal Investigator up through NHEERL Associate Director for Health or Ecology

Responsibilities

- Detailed responsibilities outlined for:
 - Principal Investigator
 - Branch Chief
 - Division Human Research Officer
 - Division Director
 - Director, NHEERL Human Research Protocol Office
 - NHEERL Associate Director for Health or Ecology
 - All NHEERL employees

Responsibilities (cont)

- Director of the NHEERL Human Research Protocol Office (HRPO) is responsible for the ethical oversight of all HSR
- Ensures that the safety and rights of all human subjects are protected.
- Advises preparation of HSR protocols
- Assists investigators and managers to understand their responsibilities
- Maintains the official records in NHEERL

Responsibilities (cont)

- Director of HRPO should be consulted for any questions about the preparation or approval of HSR protocols and should be consulted before **any studies are carried out involving human data of any kind.**
- HRPO responsible to keep comprehensive record for NHEERL of all human studies from initial approval process, through renewals, to completion of study.

Compliance with the Common Rule

- Any HSR must be reviewed by an appropriate IRB
- any organization engaged in such research must have written assurances - Federal Wide Assurance (FWA)
- Exm. - Human Studies Division (HSD) of NHEERL has an FWA, which identifies the IRB of the University of North Carolina at Chapel Hill (UNC) as its IRB of record.

Institutional Review Board

- Common Rules calls for all HSR to be reviewed by an IRB with primary goal of ensuring that the study is ethical and safe
 - Respect for persons
 - Beneficence
 - Justice

Institutional Review Board (cont)

- Approve, require modifications or disapprove all research activities
- Either by full or expedited review (for minimal risk studies or minor changes to a previously approved study)
- Continuing review of research at least once per year

Institutional Review Board (cont)

- Has authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects
- Even if an IRB declares a study exempt from the Common Rule, the Agency Human Subject Research Review Official makes the ultimate determination

NHEERL Human Research Guidance

- Applies to all studies conducted by NHEERL investigators, supported by NHEERL either through funding or the provision of facilities and services (e.g. through cooperative agreements, contracts, or grants)
- A “how to” manual for the preparation and initial review of the protocol package in NHEERL
- First decision – does study meet the definition of HSR?
- Human subjects? Research?
- Determination made by the NHEERL HRPO Director

Questions?

RESEARCH & DEVELOPMENT
Building a scientific foundation for sound environmental decisions

Part 2

Human Research Guidance: A Closer Look

Typical NHEERL HSR Protocol Package

- **Consent Form** - a process, not just a form voluntarily decide whether or not to participate
- **Initial EPA Reviews** - statisticians, scientists, or medical personnel, etc
- **Extramural Scientific Reviews** -
 - scientific merit
 - the value added by conducting human research rather than animal or in vitro research
 - issues of ethics, participant safety, and participant risks

Typical NHEERL HSR Protocol Package (cont)

- **Fact Sheet** - non-technical, jargon-free style for internal EPA use and by the EPA Office of Public Affairs
 - Impact Statement - why important to Agency
 - Background for study
 - Study Description
 - Timeline
 - Contact

Typical NHEERL HSR Protocol Package (cont)

- ***Study Justification Document***
 - Relevance to the Agency's mission
 - Why existing animal or tissue studies are insufficient
 - Anticipated public health benefit
 - Value added to decision-making

Typical NHEERL HSR Protocol Package (cont)

- **IRB Approval Documentation**
 - all correspondence START to FINISH
- **Training Certificates**
 - all study staff involved in the design, conduct of study or data analysis

Human Controlled-Exposure Studies

- Deliberate exposure by any modality that may include inhalation, ingestion, intravenous administration, dermal exposure or other methods
- As risks increase to subjects, potential benefit to society must be more compelling

Human Controlled-Exposure Studies

- Will not be initiated unless prior data:
 - Toxicity testing in laboratory animals
 - Other human exposure research, such as epidemiologic studies or controlled human exposures.
 - Studies of a very closely related chemical compound
- Pollutant Selection and Administration Criteria

Human Controlled-Exposure Studies: Dosing

- Calculations presented which document the pollutant dose that a typical subject will receive
- Compared to doses that a typical individual would be exposed to in the environment
- Maximal allowable doses calculated
- Delivered by an on-site engineering support contractor with rigorous QA/QC procedures for accuracy and reproducibility

Human Controlled-Exposure Studies:

Special Review

- • **Medical Review** - controlled exposure to pollutants, procedures which involve significant physical risk to subjects (e.g. bronchoscopy, methacholine challenge)
 - Known risks identified
 - Measures to reduce risk are in place
- – Appropriate medical criteria in place for selection of the proposed study subjects
- Team qualified to deal with any adverse events

Epidemiological Studies

- Considerations
 - Participant Burden
 - Community-based observational studies need communications plan for planning stages, for conducting the study and for sharing the results
- - This plan shared with EPA Office of Public Affairs and local, state and regional offices

Genetic Studies

- Possibility of identifying individuals with a disease
- Most stringent safeguards for subject privacy and confidentiality
- Has implications on storage of specimens
 - Future genetic tests with identifiers?
 - Future genetic tests without identifiers?

Levels of Review

- Peer Reviewer 1
- Peer Reviewer 2
- Statistician
- Physician
- Other 1
- Other 2

Levels of Approval

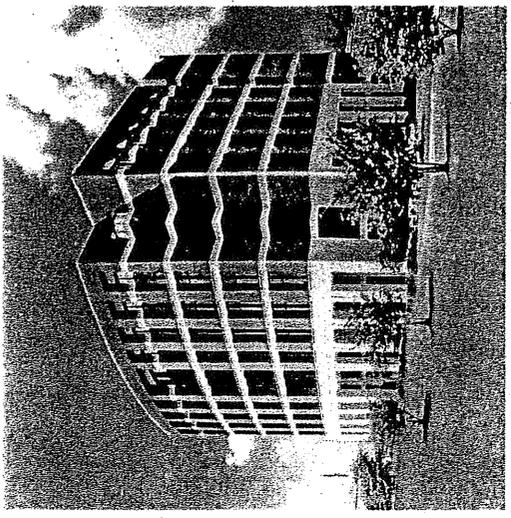
- Division Human Research Officer
- Branch Chief
- IRB
- Division Quality Assurance Officer
- Division Director
- Director of NHEERL Human Research Protocol Office
- NHEERL Associate Director of Health (or Ecology)
- EPA Human Subjects Research Review Official

NHEERL Employees as Subjects

- Strongly discouraged from conducting research on themselves
- No direct or indirect coercion of employees
- Supervisors are not allowed to ask employees they supervise to participate as subjects
- Approval and screening processes are the same



Questions???



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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF HENRY GONG

On May 17, 2005, SA DAVID L. COTNER, Special Investigations Unit, telephonically interviewed Dr. HENRY GONG, JR. (562/401-7561), Los Amigos Research Medical Science Building, Downey, CA. Reporting agent identified himself to GONG. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

GONG stated he was involved as a panel member of the Human Subjects Review Panel (HSRP) which was made up of three others who were not EPA employees. GONG stated the visit to EPA's Research Triangle Park, NC facility was his first in an HSRP review role. GONG recalled HSRP looked at incidents involving two principal investigators, including the study of human subjects who were over-exposed to di-2ethylhexyl sebacate (sebacate) from Dr. CHONG KIM's study. GONG stated HSRP's charge was to check out the details and facts and make recommendations to EPA. GONG stated HSRP did, and Dr. PRENTICE, the chairman of HSRP, had the most responsibility ensuring that happened.

GONG could not recall the actual concentration of sebacate the subjects received from KIM's study. GONG stated he did not see an attempt by EPA to cover-up anything from KIM's study. GONG opined to the contrary, the fact EPA brought in an outside group deemed experts showed EPA was open with the facts and a review process. GONG stated the recommendations made by HSRP created more bureaucracy for EPA to follow. GONG added the Institutional Review Board was also notified by EPA of the over-exposure of sebacate. GONG opined that was the opposite of what EPA would have done if they tried to cover-up the incident. GONG did not recall Dr. LINDA BIRNBAUM having any influence with the HSRP.

GONG stated when HSRP was having deliberations, most EPA people left the room. GONG could not recall or identify what EPA personnel remained in the room, but stated they did not

Investigation Conducted on: May 17, 2005	Conducted at: Telephonic
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 17, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>

interfere or participate in any way with HSRP's deliberations.

GONG stated it was 'refreshing to see EPA open-up like this'. GONG stated EPA was 'as forthright as they could be'. GONG stated EPA wanted the details of the over-exposure of sebacate known to see if there was anything EPA should be doing to avoid an accidental over-exposure of a substance in the future. GONG again stated EPA did not impede HSRP's review. GONG stated HSRP talked to multiple people and EPA did not interfere when HSRP requested further documents or to interview people who were not initially known to HSRP from the materials EPA gave HSRP.

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**OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS**

INTERVIEW OF KERM HENRIKSEN

On May 23, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. KERM HENRIKSEN (301/427-1331), Human Factors Advisor for Patient Safety, Department of Health and Human Services, Agency for Healthcare Research and Quality, Center for Quality Improvement and Patient Safety, 540 Gaither Road, Rockville, MD. Reporting agent properly identified himself to HENRIKSEN. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

HENRIKSEN stated he was involved as a panel member of the Human Subjects Review Panel (HSRP) which was made up of three others who were not EPA employees. HENRIKSEN stated the review of Dr. CHONG KIM's di-2-ethylhexyl sebacate (sebacate) study and the over-exposure of sebacate given to subjects of KIM's was his first as an HSRP member. HENRIKSEN stated he was part of the HSRP because of his expertise of understanding human error as a result of human factors in the environment. HENRIKSEN described the process as a normalization of deviance. HENRIKSEN defined this as "the margin of safety became narrower in advance of an adverse event as steps progressed because nothing happened previously". HENRIKSEN stated an adverse event could eventually occur. HENRIKSEN provided examples of the space shuttle Challenger and Columbia.

HENRIKSEN stated he had the sense EPA focused on KIM as the Principal Investigator (PI) as the cause of the error. HENRIKSEN believed it was more of a comparison of the PI versus systemic errors of the process. HENRIKSEN stated EPA was responsive to his review, but stated he understood KIM's privileges to conduct human studies were removed.

HENRIKSEN stated he could not recall the amount of exposure of sebacate the subjects of KIM's study received. HENRIKSEN stated that was not his area of expertise and he could not

Investigation Conducted on: May 23, 2005	Conducted at: Rockville, MD
Conducted by: SA David L. Cotner	OI File No: 2005-0002
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provide an answer.

When asked if he viewed any actions by EPA as a cover-up, HENRIKSEN stated "No, I didn't". HENRIKSEN recalled the HSRP was sworn to confidence, but could not state so conclusively. HENRIKSEN stated EPA, HSRP and the University of North Carolina Institutional Review Board were present during the review. HENRIKSEN's conclusion was it would be hard to establish a cover-up with that many people involved in the review process. HENRIKSEN stated the only thing he recalled as not discussed during the review was the punishment of the PI (because of privacy reasons). Otherwise, HENRIKSEN stated HSRP had access to data and people in addition to what EPA provided. HENRIKSEN stated he did not recall Dr. LINDA BIRNBAUM, and stated he did not perceive anyone from EPA objecting or interfering with HSRP.

HENRIKSEN was asked to review a copy of the letter given to the subjects notifying them of the over-exposure of sebacate from KIM's study. HENRIKSEN recalled he had access to the letter — during HSRP's review. HENRIKSEN reviewed the letter to refresh his memory and opined it did provide full disclosure and included "familiar language". HENRIKSEN noted the letter also contained a point of contact for questions and follow-up.

HENRIKSEN stated he did not know or recognize the name Dr. TED MARTONEN.

HENRIKSEN stated the only feedback he had from his role with HSRP was the review only lasted a few days. HENRIKSEN stated he felt he could have had more time to prepare reports. HENRIKSEN noted the report was a group effort of the four panel members who created individual pieces of the report and put a final product together.

HENRIKSEN stated overall, he was impressed with the EPA people he met and their concern for the incident of over-exposure involving KIM. HENRIKSEN stated he had the sense EPA people were open to the process.

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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF MICHAEL GARGAS

On May 17, 2005, SA DAVID L. COTNER, Special Investigations Unit, telephonically interviewed Dr. MICHAEL L. GARGAS (937/427-4293), The Sapphire Group, Inc., Dayton, OH. Reporting agent identified himself to GARGAS. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

GARGAS stated he was involved as a panel member of the Human Subjects Review Panel (HSRP) which was made up of three others who were not EPA employees. GARGAS stated he couldn't comment on the specific amount of sebacate di-2-ethylhexyl sebacate (sebacate) given to subjects of Dr. CHONG KIM's study without notes from the 2002 HSRP review. GARGAS didn't believe he was allowed to keep his notes from the HSRP study. GARGAS stated he could not remember the amount of sebacate the subjects were exposed to. GARGAS stated the amount of one hundred times exposure of sebacate to subjects of what they consented to receive could have been the amount, but GARGAS recalled that one hundred times the amount consented to receive seemed high.

When asked if he thought there was an EPA cover-up of the over-exposure of sebacate, GARGAS' reaction was "Nah, baloney". GARGAS stated the fact EPA asked for a review from the outside was not indicative of a cover-up. GARGAS stated the HSRP reviewed a "ton of material" before writing a report.

GARGAS stated Dr. LINDA BIRNBAUM did not interfere with HSRP's review. GARGAS stated he knew BIRNBAUM personally from a professional relationship and would have known if she was interfering. GARGAS did not recall BIRNBAUM's presence during HSRP's review. GARGAS stated had BIRNBAUM tried to influence the HSRP review, it would have been while GARGAS was there, and GARGAS did not recall any interference.

Investigation Conducted on: May 17, 2005	Conducted at: Telephonic
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 18, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>

GARGAS recalled reviewing the letter sent to notify subjects of KIM's study who were over-exposed to sebacate as part of the HSRP review. While unable to recall the specific contents of the letter, GARGAS did not recall anything unusual about the notification. GARGAS stated had HSRP believed there was anything out of the ordinary contained in the notification letter, HSRP would have noted it in the report. GARGAS recalled the letter stated the level of exposure of sebacate the subjects received and the consequences of the over-exposure.

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**OFFICE OF THE INSPECTOR GENERAL
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INTERVIEW OF ERNEST PRENTICE

On May 16, 2005, SA DAVID L. COTNER, Special Investigations Unit, telephonically interviewed Dr. ERNEST D. PRENTICE (402/559-6045), Associate Vice Chancellor for Academic Affairs, University of Nebraska Medical Center, Omaha, NE. Reporting agent identified himself to PRENTICE. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

PRENTICE stated he was the chairman of the Human Subjects Review Panel (HSRP) which was made up of three others who were not EPA employees. PRENTICE recalled EPA management had shut down the study of human subjects who were over-exposed to di-2ethylhexyl sebacate (sebacate) from Dr. CHONG KIM's study after EPA learned of the over-exposure. PRENTICE stated that occurred prior to the HSRP visit during the summer of 2002. PRENTICE opined EPA's review was thorough and recalled EPA was forthcoming in giving HSRP documents to conduct the review. PRENTICE recalled EPA also allowed HSRP to review additional documents and interview additional people requested by HSRP members. PRENTICE stated HSRP was not denied access to anyone.

PRENTICE did not believe there was any intention by EPA to hide the fact that an over-exposure of sebacate was given to subjects in excess of what they consented to receive. PRENTICE stated he could not refer to any documents from HSRP because they were turned into EPA at the conclusion of the HSRP. PRENTICE stated if HSRP wanted to review something and they were denied access, he would have remembered the circumstances. PRENTICE could not recall any interference or denial of access to EPA documents or people by EPA officials. When PRENTICE was asked if he recalled any interference from Dr. LINDA BIRNBAUM, PRENTICE stated he remembered her and DAN NELSON (from the University of North Carolina), but BIRNBAUM did not interfere with the HSRP.

Investigation Conducted on: May 16, 2005	Conducted at: Telephonic
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 17, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>

PRENTICE emphasized he would recall any interference with the HSRP review, because he had reviewed other programs (not EPA) which had 'stone-walled' the reviewers and had attorneys present for every person talked to by the review panel. PRENTICE emphasized that was not the case with EPA. PRENTICE stated the HSRP had the authority to go to the Attorney General if the HSRP thought there was any level of non-cooperation or cover-up by EPA.

PRENTICE could not recall the amount of sebacate given to the subject's of KIM's study. PRENTICE recalled the conclusions of the HSRP were given to EPA management. PRENTICE stated the research program's re-instatement meant EPA had taken corrective action to resolve the causes that lead to the over-exposure of sebacate to the subjects above what they consented to receive.

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OFFICE OF THE INSPECTOR GENERAL
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INTERVIEW OF RICHARD P. HERMANN

On May 5, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. RICHARD P. HERMANN (919/966-6217), Director, Human Studies Division (HSD), National Health and Environmental Effects Research Laboratory (NHEERL) at his office, room number 158, located at the EPA Human Studies Facility, 104 Mason Farm Road, Chapel Hill, NC. HERMANN was shown proper identification by reporting agent. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC), alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

HERMANN was not an EPA employee in 2001 when the incident involving the over-exposure of Dr. CHONG KIM's study was detected. HERMANN began his employment with EPA during January 2005.

HERMANN's position had oversight of KIM's study, and as a result, HERMANN had extensively reviewed the material of what was done as a result of the over-exposure. HERMANN opined an 'enormous time' was spent on checking the calculations and making the corrections. HERMANN opined there was an aggressive full disclosure of the problems associated with the study and ready access was provided for review. HERMANN did not believe there was any cover-up or attempt to hide what happened.

HERMANN opined the dosage levels actually received by the subjects of KIM's study were below dangerous levels. HERMANN believed EPA and the HSD incorporated lessons learned from the KIM incident into policy for NHEERL. HERMANN stated there are now up to six levels of review and nine levels of approval.

Investigation Conducted on: May 5, 2005	Conducted at: Chapel Hill, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 5, 2005	Prepared by: SA David L. Cotner <i>DL</i>

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OFFICE OF THE INSPECTOR GENERAL
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INTERVIEW OF RICK LINTHURST

On May 3, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed RICK LINTHURST (919/541-4909), Science Advisor, OIG, in the OI section at the EPA Facility at Research Triangle Park (RTP), NC. LINTHURST was shown proper identification by reporting agent. LINTHURST was familiar with OI's investigation into alleged misconduct by CHONG KIM and was requested to provide information to support OI's investigation into allegations Dr. TED MARTONEN, EPA Employee, made to the Office of Special Counsel, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of KIM.

LINTHURST stated di-2-ethylhexyl sebacate (sebacate) was a substance used as a control for this experiment, as he interpreted it from reviewing the Human Studies Division (HSD) PM document put together by the National Health and Environmental Effects Research Laboratory (NHEERL) to assist the Institutional Review Board (IRB) and the External Review Panel study. LINTHURST received the document from Dr. HAROLD ZENICK, Associate Director for Health, Office of Research and Development (ORD), National Health and Environmental Effects Research Laboratory (NHEERL). The document appeared to have some pages out of order. LINTHURST also provided a copy of the USEPA Human Subjects Review Panel Site Visit Report, dated August 21, 2001 (Attachment 1), also received from ZENICK. After reviewing the documents, LINTHURST stated sebacate was a normal control in the scientific world. As LINTHURST understood the study, the test was on particle matter size in an aerosol form. The particle matter was sebacate. LINTHURST identified the sebacate as an inert substance where particle size was changed to see where the particle settled in and on the lungs, and to see the impact of where it was deposited and the deposit of the sebacate was an issue. LINTHURST understood KIM's study was interested in numeric deposits, not exposure (of particle size increase), of sebacate.

LINTHURST also provided a copy of the Human Studies Evaluation and Corrective Action Plan (HSECAP), (Attachment 2), also from ZENICK. The HSECAP was prepared by Dr. LAWRENCE REITER, Director, NHEERL, and dated August 28, 2002. LINTHURST stated the HSECAP was a response to the Site Visit Report. LINTHURST stated the HSD PM also

Investigation Conducted on: May 3, 2005	Conducted at: Research Triangle Park, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 3, 2005	Prepared by: SA David L. Cotner <i>DL</i>

contained copies of the notice given to the human test subjects and the notification letters sent to the human test subjects, as well as a detailed time-line. LINTHURST stated his review of the HSD PM showed the human test subjects were told they were given 1/20th of a dose and that they could receive up to 20 times that amount. LINTHURST was unable to specify how those numbers were developed. LINTHURST stated the HSD PM stated the experimentation was not a human health issue.

LINTHURST believed there was not an annual review completed since the external peer review panel in August 2002, as the report stated it would be required every three years, as told by ZENICK. ZENICK indicated to LINTHURST that another review would begin in the near future.

LINTHURST opined, after reviewing all three reports, he did not believe there was a cover up by EPA to conceal any wrong-doing related to KIM's study. Instead, LINTHURST did note this was KIM's second error, and that he had been warned previously for errors related to conducting human studies. LINTHURST stated KIM can no longer do human exposure work because the violation related to this matter was his second violation. LINTHURST also noted KIM made changes to the studies design without finding errors to the study.

LINTHURST stated ZENICK was responsible for notification to the subjects of the human testing of the increased amount of sebacate they received.

LINTHURST stated REBECCA CALDERONE, a Division Director located in Chapel Hill, NC, and whose predecessors were Drs. BIRNBAUM and VANDENBERG, would have log books related to KIM's sebacate study.

LINTHURST opined PAUL GILMAN, former Assistant Administrator until about five months ago, would not have a lot of information related to this matter. LINTHURST believed GILMAN was currently in Oakridge, TN. LINTHURST opined ROGER CORTESI of PREUSS' office in Washington, DC could have useful information of the correspondence between GILMAN and MARTONEN.

LINTHURST referred the reporting agent to ZENICK for copies of MARTONEN's correspondence to and from the EPA Administrator. ZENICK had oversight of KIM's study on human subject's. ZENICK would also have information on EPA guidance on human subject experimentation. LINTHURST also stated ZENICK may be able to identify the technician who identified the dosage error of KIM's study.

LINTHURST stated PETER PREUSS, Director, National Center for Environmental Research and Quality Assurance, ORD, headed the EPA review and would have further information on Human Subject testing. LINTHURST also added DR. REITER was the NHEERL Lab Director at the time and was ZENICK's boss. LINTHURST referred reporting agent to KAREN PALMER, Office of General Counsel, for further information and background of lawsuits MARTONEN had against EPA.

Attachments

1. Copy of the USEPA Human Subjects Review Panel Site Visit Report, dated August 21, 2001
2. Copy of Human Studies Evaluation and Corrective Action Plan, dated August 28, 2002

**U.S. Environmental Protection Agency
Human Subjects Review Panel**

Site Visit Report

**Human Studies Division
National Health & Environmental Effects
Research Laboratory
Chapel Hill, North Carolina**

August 21, 2002

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INTRODUCTION

The Human Subjects Review Panel (HSRP) was formed by EPA after it was discovered that two research projects involving human subjects within the National Health & Environmental Effects Laboratory's (NHEERL) Human Subjects Division (HSD) had dosing errors. The two projects were the: 1) Bromodichloromethane (BDCM) Study and, 2) Particulate Matter (PM) Study. These errors led to the subjects being exposed to higher levels of materials than were specified in the respective research protocols including the informed consent forms.

Each HSRP member was charged with:

- Reviewing the policies, procedures, and methods used by the HSD in research involving human subjects. Specific points to be covered in the report were: (i) whether the policies, procedures and methods for research with human subjects are adequate and if not make recommendations for making them so, and (ii) to compare how the division's policies, procedures and methods compare with national practice for research involving human subjects.
 - Travel to North Carolina to make this assessment both by personal observations and by conversations with EPA and University of North Carolina staff and Management, specifically addressing the two projects where dosing errors were made.
- Modifying their individual reports at the end of their discussions with one another.

In addition, the chairman of the panel was asked to lead and guide the panel's discussion and the investigative process, and to write a summary of the HSRP's discussions and findings. The HSRP's reports follow.

II. HUMAN SUBJECTS REVIEW PANEL

This report was prepared by Human Subjects Review Panel (HSRP) Members for the Environmental Protection Agency on August 21st, 2002. Panel members were:

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I. SITE VISIT CHRONOLOGY

August 19, 2002

Introduction

- A. Dr. Preuss
- B. Dr. Reiter
- C. Dr. Vandenberg

Dr. Teresa Leavens Interview

Laboratory Tour

Dr. Chong Kim Interview

Mike Ray Interview (with Dr. Vandenberg and Dr. Devlin)

August 20, 2002

Institutional Review Board (IRB) Introductions and Discussion

Discussions with Dr. Vandenberg and Staff

Report Writing Session

Individual Report Presentation and Discussion

August 21, 2002

Report Review and Discussion

Report Revision Session

Exit Briefing

IV. PANEL MEMBER REPORTS

This section presents the individual reports of the four panel members:

Dr. Ernest Prentice
Dr. Henry Gong
Dr. Michael Gargas
Dr. Kerm Henriksen

**U.S. Environmental Protection Agency (EPA)
Human Subjects Review Panel (HSRP)
Site Visit of the Human Studies Division (HSD)
National Health & Environmental Effects Research Laboratory (NHEERL)**

HSRP Member: Ernest D. Prentice, Ph.D.

EPA-HSD Investigation of Non-Compliance in Protocol 91-EPA-226 (PM Study) and 99-EPA-25 (BDCM Study)

The incident time line for the PM protocol indicates that officials at HSD and NHEERL took timely action to suspend all studies by the responsible PI with notification of the IRB the day of suspension (8/17/01). The incident was thoroughly investigated but was hampered by difficulties encountered in dose calculations further complicated by personnel issues. However, preliminary dose calculations indicated that no subject had been placed at risk, which was ultimately verified by independent review. Thus, there was not a compelling reason from a risk-disclosure standpoint to notify all subjects immediately in the absence of firm data. Nevertheless, an interval of 8/17/01 to 6/06/02, which is the date of notification of subjects, appears excessive. In addition, Dr. Peter Preuss (EPA Human Subjects Research Review Official and Director, National Center for Environmental Research) was not notified until April 2002. This suggests the need for the EPA to develop a well-defined, streamlined process for when and to whom non-compliance should be reported along with timely, efficient action relative to the protection of human subjects.

The incident time line for the BDCM study also indicates that officials at HSD and NHEERL took timely action. In this case, all clinical HSD studies were suspended (6/21/02) and a comprehensive investigation commenced with HSRP members identified 7/24/02 to perform an external review. Letters of notification were sent to subjects 7/26/02.

An incident response comparison between the two incidents of non-compliance clearly indicates that all involved EPA administrative personnel were concerned about strengthening the HSD's program for protection of human subjects beginning with the first incident. However, the reasons for this concern were obviously enhanced when the second incident of non-compliance occurred less than one year after the PM study problem. To this end, existing policies and procedures were aggressively re-examined and new policies proposed.

Risk Assessment for the PM and BDCM Studies

There are no data to indicate that any subject in the PM study or the BDCM study was ever placed at immediate or long term risk as a consequence of exposure to materials in excess of the doses allowed by the IRB-approved protocols and stated in the consent documents. No subject to date has reported any adverse event (AE) which he/she thinks may be related to participation in the aforementioned studies. The risk issue was carefully reviewed by multiple experts and the IRB agreed with the absence of risk conclusion. This panel member also agrees.

Assessment of Current and New Policies and Procedures

The new (expanded) policies and procedures (dated 8/1/02) are designed to minimize the possibility that protocol deviations may occur in the future during HSD studies. While this panel member will not offer comment on all of the policies and procedures which should be implemented and refined as necessary, there are action items that warrant comment as follows:

Quality Assurance/Quality Control

It is critical that appropriate quality control (QC) mechanisms be in place for the preparation and delivery of particulate matter pollutants in any future HSD inhalation studies. No subject should be enrolled in any study unless there is accurate measurement of dosing with ongoing QC accuracy checks. The situation which existed in the PM incident, where the HSD was unable to quickly extract the necessary data from the software in order to calculate doses given to individual subjects is obviously a concern. The QC component of the Corrective Action Plan, if implemented properly, should correct this serious deficiency. In terms of the evaluation of the QA/QC Plan, I yield to other panel members with more expertise in this area who will comment. Finally, the same QA/QC considerations apply to non-inhalation studies although the Plan to utilize the investigational drug pharmacy and very specific SOPs should minimize the possibility of future dosing problems.

Protocol Management

The role occupied by Dr. Elston Seal is both critical and central to the proper development and conduct of HSD clinical studies. Since Dr. Seal will retire shortly, it is essential that a suitable replacement be found. Serious consideration should be given to the suggestion in Dr. Stephen Bernard's letter of 9/26/01 that a centralized "protocol office" be established to facilitate investigator submission to the IRB, revision of protocols, amendments of consent forms, and general record keeping. This office, if established, should be staffed by an administrator who is at least familiar with the requirements of the common rule, protocol development, and IRB requirements. This would free up Dr. Seal's replacement to become more involved in programmatic issues and less involved in paperwork flow.

Peer Review

The HSD policies and procedures call for scientific peer review by two scientists. Consideration should be given to obtaining the scientific reviews prior to IRB review. While there is no regulatory requirement, such reviews often facilitate IRB consideration of the protocol.

Audits

It is important for the HSD to periodically re-review/audit clinical studies to identify and correct problems as well as improve the protocols.

Consent Process

The consent process as described in the HSD policies/procedures as well as by HSD personnel is in compliance with 40 CFR 26.116 which addresses the circumstances under which consent should be obtained. The integrity of the consent process should continue to be emphasized at HSD. Utilization of a consent auditor can be very helpful in identifying ways in which the consent process can be improved.

Consent Forms

The consent forms for the PM study (6/26/01 - 6/26/02) and the BDCM study (4/1/02 - 4/1/03) are in compliance with 40 CFR 26.116(a)(b). The following are, however, suggestions for consideration:

- Simplify the language, particularly since the HSD subject population is changing to include more elderly subjects.
- Add a subject's initial blank at the bottom of each page which helps the documentation.
- Add an investigator's certification (concluding consent) statement for his/her signature.
- Expand the subject's certification (concluding consent) statement for his/her signature.
- The consent forms should list all investigators and their phone numbers. In addition, for invasive studies, involving more than minimal risk, consideration should be given to listing a 24-hour contact number on the consent form. The subject should always have access to a contact who can respond to concerns of a medical nature or otherwise.

IRB Review and Oversight

The UNC College of Medicine IRB is the IRB of record for the HSD. In the opinion of this panel member, the IRB performs a substantive review of HSD protocols, consent documents, amendments, and AE reports. Based upon the documentation reviewed and the interview with Dr. Stephen Bernard, Dr. Daniel Nelson, and Dr. Ernest Kraybill, it is clear that the IRB is one of the strengths of the HSD program for the protection of human subjects. It also should be mentioned that the UNC IRB is nationally recognized. The IRB, in turn, recognizes and acknowledges the value of its relationship with the HSD and a comfort level attributable to the HSD QA/QC initiatives. In view of this relationship and the fact that Dr. Peter Preuss is the designated Institutional Official (IO) on the soon-to-be submitted HSD Federal Wide Assurance (FWA), this panel member recommends that the IO be provided with copies of IRB minutes pertinent to HSD protocols.

Establishing a Safety Culture

It is important for the HSD to continue the current emphasis on the development and maintenance of a culture of compliance. It is clear that the senior administration is committed to this goal.

Conclusion

In this panel member's opinion, the HSD's program for protection of human subjects, conditional upon implementation of the proposed "new expanded" policies and procedures, will be entirely satisfactory and will meet current national standards.



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**U.S. Environmental Protection Agency (EPA)
Human Subjects Review Panel (HSRP)
Site Visit of the Human Studies Division (HSD)
National Health & Environmental Effects Research Laboratory (NHEERL)**

HSRP Member: Henry Gong, Jr., M.D.

EPA-HSD Investigation of Non-Compliance in Protocol 91-EPA-226 (PM Study) and 99-EPA-25 (BDCM Study)

The EPA/HSD performed timely, serious, and expeditious investigations following their notification about the incidents. However, there was an apparent delay of several months for EPA headquarters (ORD) to be informed by the local EPA (a decision by the local supervisors). More rapid responses occurred in the BDCM study in which notification took place immediately. In both incidents, the local UNC IRB was informed immediately by EPA. The IRB essentially went along with the responses of the HSD and ORD and remained in continuous communication with the EPA (E. Seal).

The EPA was very engaged, thorough, honest, and resolute in its investigation and responses:

- An immediate shut down of both studies and all EPA clinical protocols was instituted.
- Consultations about the two incidents (re: protocol, data, subject safety) were obtained from intramural and extramural parties, including CIIT and, eventually, this panel (HSRP).
- Correspondence and coordination between the EPA and the IRB occurred, including the appropriate content of the notification letter to subjects.
- The senior EPA PI was suspended from clinical studies in the EPA.
- Vulnerability studies were done for two incidents and other studies in EPA.
- A new EPA general research policy was developed and instituted.

Risk Assessment for the PM and BDCM Studies

No immediate or long-term adverse health effects were expected from both studies. None have been reported or documented. The calculated mass deposition of inhaled DEHS in the lungs was not expected to cause adverse health effects, based on the calculated dose, literature (abundant prior studies with the DEHS), experience, and lack of subject-reported symptoms. The followup of as many subjects as possible was conducted (and is ongoing). No adverse medical effects or complications were reported or documented in any subject thus far. The notification letter was accurate, informative, and timely (except for the PM study). Latter 10-month delay was related to complex PI dose calculations and external-party modeling, interpretation issues, consultants' schedules, disciplinary actions, development of notification letter, etc. (per Dr. J. Vandenberg, 8/20/02).

Assessment of Current and New Policies and Procedures

The revised General Policy Guidelines for Conduct of Human Research at the NHEERL appears to be an excellent beginning and reflects the serious priority of human subject protection. The Guidelines and related policies, procedures, and discussions with EPA and IRB representatives clearly indicate that the EPA has made subject safety a primary concern and the focus of corrective actions (see below). Immediate/recent responses by EPA indicate recognition and serious application of human subject protection:

- EPA requires research ethics training which is greater than that required by the IRB.
- The proposed mentoring system will enable the passage of data, knowledge, and experience. It is well received and supported by EPA staff and management.
- More levels of peer review and approval of research protocols and safety measures will minimize unsupervised revisions and "surprises."
- More attention to signed informed consents (by PIs and Nursing Staff) will improve the informed consent process.
- Adding new investigators and personnel to consent forms must be routinely done, along with resolving related training and certification issues.
- More frequent and unannounced QA audits were discussed to sensitize the investigators.
- Pharmaceutical Scientist will prepare solutions, as appropriate. (QC check for safety)
- Peer scientist will observe PI in certain types of experiments (non-contractor projects). (QC check for safety)
- Amendments to protocol and/or consent forms now have more systematic EPA review and approval process (especially the major amendments) prior to IRB submission (more affirmative review and recognition by EPA management).
- 5-year limit for protocols to be wholly re-submitted to EPA (and IRB?).
- Access to medical care from EPA doctors is possible at all times (even off hours; 24/7), e.g., paging.
- Dry runs prior to human subject participation should include the chemical or pollutant of interest to specifically measure and double-check the dose calculations, as well as the time-activity checks.
- Subject safety is being further emphasized by the EPA by involvement and commitment by senior EPA management.

In summary, my understanding is that the above items are reasonable and will positively impact research and safety review, quality control and assurance, and the informed consent process. The result will (hopefully) significantly reduce errors and inattention to details and minimize adverse human events in at least the short-term.

IRB Review and Oversight

In general, the UNC Medical School IRB appears to be an excellent IRB with strong leadership and understanding and practice of human subject protection. The IRB has had a strong research relationship with the EPA since the mid-1970s. The IRB representatives indicated their high respect and confidence in the EPA's review process, QA system, and PIs/staff. The IRB representatives indicated that the IRB and EPA were in frequent communication from the get-go

about both incidents. Correspondence documents this ongoing relationship. Some specific areas strategic EPA-IRB interactions:

- Minutes with discussion. Written discussions are not included in old Minutes. IRB representatives state that this is changing, i.e., more written discussion will be included.
- Protocol review. No pulmonologist is a member of the IRB, but questions have been asked by members regarding EPA submissions. Pre-submission EPA scientific review(s) will strengthen the confidence of the IRB's review (desired by the IRB).
- Informed Consent Form (ICF) review. Readability might be improved in certain complex or technical protocols or those involving less educated lay people. Certification statements of signatures would be helpful to confirm the subject's understanding of the consent process.
- Continuing review. Expedited reviews of (major) amendments were performed in the PM study. This probably was inappropriate, per the IRB Chair. The IRB is now reducing expedited reviews and referring the submissions to the full IRB.
- Compensation. No comment.
- Consent process. Current EPA recruitment process was explained and appears reasonable. Missing link is confirmation of signed consent form and that should be corrected by having the nurses actively involved in verifying the signatures. I suggested a check list for all involved. Not clear how this is being reviewed by the IRB.
- Consideration of EPA requirements. The IRB representatives expressed their high regard for the EPA's review process, high-quality QA and science, and continuing relationship as the EPA's IRB of record. The IRB representatives did not express any negative issues about the EPA. They had not as yet received a copy of the draft EPA general research policy. The IRB will await the EPA's deliberations regarding the shutdown of its clinical research program.

Clearly, this IRB recognizes its limitations and challenges for improving its review process. The IRB appears receptive to suggestions for improvement and prefers support in its reviews, e.g., scientific reviews.

Conclusions

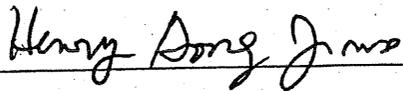
The EPA/HSD human research program has a national and international reputation for high quality research in human health effects. The human research program remains an integral component of the EPA's mission and a model with decades of experience and accomplishments. The two non-compliance incidents appear to be exceptions rather than the rule. The EPA acted appropriately and with due diligence in responding to and investigating the incidents. In one case, the process of notification of subjects could have been much better and faster. I believe that the EPA human research program and human subject protection will be significantly strengthened by the revised EPA policies and procedures which create an expected environment and culture of both "checks and balances" and "safety first." In addition, the UNC IRB can make its decisions with greater confidence and trust with the EPA.

This is not to say that future "human errors" will not occur despite the institution of the policies, etc., but they should help reduce incidents during the short term. Longer-term benefits will need

continued vigilance, re-education, and EPA management's commitment to this unending process of human subject protection.

Recommendations

- IRB minutes should go to Peter Preuss (EPA Institutional Official).
- Increased accessibility (24/7) of study physicians for subjects, e.g., pagers.
- Check list of required screening procedures and activities, including signed consent form.
- Consider a "protocol office" to reduce errors (per IRB letter, 9/26/01).
- Chemicals or pollutants should be measured in preliminary studies (without subjects) as part of either "dry runs" or QC-runs.
- Scientific reviews (including safety assessments) can be done pre-IRB submission. This assists both the EPA and the IRB in decision-making.
- Emphasize the calculated and measured human dose and health effects (if any) in research applications and the permissible dose range in the protocols and consent forms.
- Streamlined process for notifying all levels of EPA management of non-compliance incidents needs to be developed and implemented.
- Continue with finalizing EPA General Policy Guidelines for Conduct of Human Research at NHEERL. Implement soon!



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**U.S. Environmental Protection Agency (EPA)
Human Subjects Review Panel (HSRP)
Site Visit of the Human Studies Division (HSD)
National Health & Environmental Effects Research Laboratory (NHEERL)**

HSRP Member: Michael L. Gargas, Ph.D.

Risk Assessment for the PM and BDCM Studies

PM Study

Notification Letter for Subjects, Timeliness Issues. The notification letters to the subjects in the PM study were sent out about 10 months after the protocol violation was identified. EPA staff indicated that this delay was due to the negotiations involving disciplinary action with the PI, the complexities of calculating the actual doses received by the participants, and the verification of doses by an outside evaluation. This length of time seems excessive and efforts should be made by EPA to expedite this process in the future.

Follow-up with Subjects. The tracking system in place and follow-up with subjects seems to be adequate based on the information provided to the HSRP in the document "HSD's Steps In Contacting Subjects." No other suggestions are made to the EPA to improve this process.

Long Term Effects. The maximum dose to subjects was calculated to vary from 0.89 to 2.69 mg of di-2-hexyl sebacate. The PI's approach to estimating dose was verified by outside experts at CIIT. Dr. Bennett of UNC made a comparison of the PI's doses to doses of the same material received by human subjects (with no adverse effects) in other studies. It was concluded that the PI's subjects inhaled about 58% as much particle mass as the subjects in the comparison study and as such, would not be expected to experience any long term adverse effects.

BDCM Study

Notification Letter for Subjects, Timeliness Issues. The notification letters to the subjects in the BDCM study were sent out about one month after the protocol violation was identified. Time to notification of subjects in this instance is considered excellent by this reviewer.

Follow-up with Subjects. The tracking system in place and follow-up with subjects seems to be adequate based on the information provided to the HSRP in the document "HSD's Steps In Contacting Subjects." No other suggestions are made to the EPA to improve this process.

Long Term Effects. The protocol violations resulted in 6 out of 10 subjects exposed orally up to 260 ng BDCM/kg-bw and to dermal doses in 10 out of 10 subjects up to 107 ng BDCM/kg-bw. The chronic Reference Dose (RfD), a daily dose that a person can be exposed to for a lifetime with no expected adverse effects, is 20,000 ng/kg-bw/day for BDCM. The RfD is orders of magnitude above the single doses inadvertently received by the subjects in the BDCM project.

Therefore, the subjects are not anticipated to experience any long term adverse effects from this protocol violation.

Assessment of Current and New Policies and Procedures

It is obvious that a number of the current policies and procedures were inadequate to prevent the two protocol violations that are the subject of this review. I applaud the EPA in their documentation of the problems associated with each incident and for the short term and long term actions implemented and/or proposed to correct these deficiencies as described in the documents provided to the HSRP ("Problems Identified and Solutions Implemented in Response to PM Protocol Violation" and "Problems Identified and Solutions Implemented in Response to BDCM Protocol Violation"). The proposed HSD Policies are a good start in addressing the deficiencies highlighted as a result of the two protocol violations and the EPA is encouraged to refine and finalize the new proposed protocols. The following recommendations are provided, by category, for consideration by EPA during these refinements. The recommendations listed below may or may not already be present in the proposed policies and are included here to highlight the areas of most concern to this reviewer.

SOP QA/QC

It is imperative that the stability, homogeneity and concentrations of dosing solutions be verified before exposures to human subjects are performed. This is necessary whether the PI or the Investigational Drug Pharmacy prepares the solutions. It was disconcerting that the PI assumed that the solutions for the oral and dermal BDCM studies were stable and uniformly mixed based on faith that the previous investigator performed the proper experiments, without independently verifying this assumption herself. The newly assigned PI for the BDCM protocol could not produce data to convince this reviewer that the past two PIs conducted the experiments necessary to verify the day to day concentrations and stability of the dosing solutions. The current PI indicated that it was assumed that the BDCM solutions would be reproducible and stable because they were prepared in a fashion similar to that conducted for MTBE and no problems were encountered with MTBE. This is totally unacceptable. It is strongly recommended that each chemical studied have independent verification of stability, homogeneity and concentrations of dosing solutions, no matter how similar the chemical is to previously studied materials.

Analyses of the chemical concentration of dosing solutions should be conducted on a routine basis. Measurements made every time dosing solutions are prepared would be optimal, although measurements made on a scheduled routine basis would also be acceptable. Waiting two to eight months to receive concentration data on dosing solutions is totally unacceptable.

It is recommended that an acceptable range for dosing solutions (or delivered dose) be provided for each protocol by the PI to indicate more precisely when an incorrect dosing event has occurred.

Measures of delivered dose should be included in all protocols, whether or not delivered dose is the parameter of concern.

It is recommended that independent review of all draft protocols be conducted and issues addressed prior to sending the protocol to the IRB.

Training

Routine training of all new and current staff is recommended.

Mentoring

All new PIs should be assigned a mentor for a specified period of time before being allowed to conduct independent human studies. Implementation may be enhanced if EPA can identify incentives for serving as a mentor.

24 by 7 Compliance

It seems prudent that a physician be available to all subjects 24 hours per day 7 days per week.

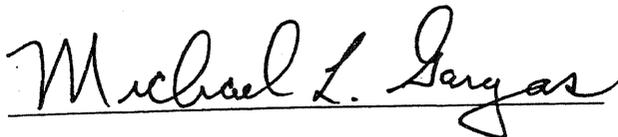
Compensation

Compensation of subjects for the procedures performed seems appropriate to this reviewer.

Conclusions

This reviewer concludes the following based on review of the materials provided and the interviews conducted on-site:

- The protocol violations have been extensively evaluated and properly characterized by EPA and the solutions implemented to date are appropriate.
- The integrity of the HSD program is not compromised by the protocol violations reviewed by the HSRP and will likely be enhanced as the proposed protocols and procedures are refined and implemented.



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**U.S. Environmental Protection Agency (EPA)
Human Subjects Review Panel (HSRP)
Site Visit of the Human Studies Division (HSD)
National Health & Environmental Effects Research Laboratory (NHEERL)**

HSRP Member: Kerm Henriksen, Ph.D.

Assessment of Current and New Policies and Procedures

Training

The writer is in complete agreement with HSD's long term plans to implement training for new investigators and refresher training for current investigators that will help maintain an on-going emphasis and awareness of subject safety issues. While training programs, in and of themselves, will not eliminate errors brought about by individual slips and lapses (i.e., inattentiveness to detail), serious investment in training programs is one way management can assure employees that a focus on following protocols and ensuring subject safety is a major strategic goal. In addition to the well described training plans for orientating new employees and visiting scholars, specific training for individual studies, continuous learning, and mentoring that is found in Volume 1, Tab 6, there are a wealth of training technologies and methodologies that can be used to enhance understanding of subject safety issues. In addition to the training programs found in Volume 1, the writer recommends that HSD consider the feasibility of employing some the following activities that will serve to augment and support current training plans:

- Use of performance enhancing technologies such a computer-based training, web-based training, and electronic performance support systems that have the capability to deliver training on short notice, when and where it is needed.
- Use of job performance aids (electronic or paper based) such as safety check lists for tasks where specific safeguards need to be in place or that involve memory sequences that are subject to forgetting.
- Use of simulations or dry-run exercises with appropriate levels of physical and psychological fidelity as a technique for training and assessing new quality control processes or rapid- pressured decision-making responses to potential subject complications.
- Create case histories or use case histories from related research projects on human subjects; web searches, NIH or NLM would be a good places to start to gather information.
- Bring in safety experts as speakers or seminar leaders from related disciplines such as complex systems and human error, clinical risk management, medical error and patient safety, human factors engineering, quality control, root-cause-analysis or failure mode and effect analysis, and implementing cultural change to expose staff to new concepts and ideas that have application to subject safety.
- As indicated in Volume 1, specific training for individual studies in terms of protocols, data or specimen collection, and other technical or equipment related aspects of the research is needed. Periodic training needs assessments need to be conducted as well as

clear standards of adequate performance with respect to technical tasks need to be established.

- Brainstorming sessions that focus on areas of potential vulnerability and the pros and cons of proposed solutions can serve as a training as well as problem solving vehicle.
- Likewise, training in the form of seminars, workshops, professional conferences, and continuing education units for upper level managers in leadership positions is recommended to gain exposure to new concepts and principles in safety science.

Mentoring

The learning that can occur from a respected, more knowledgeable and experienced colleague is an often overlooked and poorly utilized source of training and support for employees. Volume 1, Tab 6 provides a brief operational concept of how a mentoring program can be implemented in HSD. With a focus on ethics and respect for subjects and other employees, the document describes the responsibilities of the mentor, issues to be covered in a mentoring relationship, and groupings of new employees or mentees for which different qualities or characteristics of mentors are likely to be needed. The writer applauds the wise use of human capital in this fashion. Suggestions for improvement in further developing the mentoring program focus mostly in providing additional detail with respect to the following:

- Responsibilities of the mentee.
- The link between mentoring duties/responsibilities and the employee's own performance appraisal plan.
Further specification of rules of the road and pitfalls to avoid while mentoring.
Plans for assessing or evaluating how well the mentoring system is working.
- Documenting whether individual objectives and goals are being realized in mentee-mentor pairings.

24 by 7 Compliance

The suggestion that arose during HSRP discussions for having a physician or individual with medical sensitivities from HSD available on call 24 hours a day and seven days a week to respond to subject calls related to research protocols deserves serious consideration. Such an availability is currently not part of HSD's proposed new policies and procedures. While it is anticipated the actual occurrence of calls with such an availability is likely to be very low, the benefit of 24 by 7 availability is that it provides an added opportunity for quick and decisive recovery from harmful consequences should a subject experience an adverse event.

Establishing a Safety Culture

A fairly common organizational response to managing errors and violations that have increased risk to humans is to identify the individuals involved; determine their culpability; schedule them for re-training or other disciplinary measures; develop new procedures that serve as countermeasures; introduce some engineering retro-fixes or new technology that will prevent the problem; and issue proclamations to all staff to be more vigilant and attentive to safety issues. If this is all that is done, there are several reasons why this response is insufficient.

- Since people do not intend to commit errors, it is difficult for others to control what the individuals cannot control themselves.
- Accidents rarely have a single cause; they are the product of several intricately intertwined factors – individual, task, situational, equipment related, social/organizational, and managerial.
- With respect to new procedures development, closing the barn door after the horse has bolted will prevent other horses from bolting through that particular door, but there will be other doors that managers typically are not aware of.
- Most accidents have such a low probability of occurrence that managers gain a false sense of security when nothing adverse happens for a period of time; falsely attributing the safe period to the new procedures is very tempting and understandable but unwise, especially in the face of external pressures to “fix the problem.”
- Humans do not perform vigilance very well; double-checking is better than no double-checking, but it is not fail-safe.
- The greatest challenge to calls for enhanced vigilance and situational awareness is in maintaining continuous emphasis; after a period of non-events the new QC efforts start to erode and fizzle out.
- People will continue to make errors, especially of the slips, lapses, and forgetting variety. Retraining is not the answer here since such lapses are frequently of the skill-based variety that are well learned.

Since it is unlikely that some errors can be totally eliminated, a goal of effective risk management is to increase organizational resilience in detecting or making more visible errors and violations when they do occur and minimizing the likelihood of harmful consequences to subjects should they experience an adverse event. To accomplish this, a culture of safety needs to pervade all levels of the organization. High reliability organizations are those that very actively incorporate a culture of safety not by passively counting the number of days without an accident, but by actively anticipating and reaching agreement on where the other “open barn doors” may be. Convening a multidisciplinary QC or safety team that meets periodically, identifying a finite number of the most vulnerable areas, initiating improvements or corrective actions, and tracking changes across time, would represent a major step in this direction.

To ensure that a concern for safety is actively maintained on an on-going basis, such a group should explore the value of the following but not be limited to these activities:

- Determine the role management should play in creating, reinforcing and sustaining a safety culture, assuming subject safety is an organizational strategic goal of top priority
- Determine how to create an organizational climate that is non-punitive and open to a candid sharing information as a vehicle for learning
- Determine what safety lessons can be learned from other industries that deal with health hazards
- Provide recommendations for a viable mentoring system and/or QC teams
- Determine daily, weekly, monthly QC checks and monitoring activities
- Invite guest speakers to the lab that have implemented successful, on-going programs
- Identify other educational opportunities related to subject safety
- Identify process improvements

- Provide recommendations for timely communication with subjects when protocol violations occur
- Interview past subjects to assess what they understand and don't understand about the research protocols
- Determine value or feasibility of using an external consultant or company to help launch subject safety initiative
- Explore other mechanisms for promoting and sustaining an on-going safety culture.



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VI. SUMMARY OF DISCUSSION

The four members of the Human Subjects Review Panel (HSRP) discussed the individual reports presented by each member. Comment was made that the two incidents of non-compliance were aggressively and thoroughly investigated with timely engagement of appropriate EPA personnel. The data reviewed clearly indicate that a valid determination was made that no subject was exposed to either immediate or latent risks associated with the dosing errors. The "new and expanded" HSD guidelines for protection of human subjects were discussed and their importance emphasized in terms of helping to minimize the possibility of protocol deviations occurring in the future. The need for enhanced QA/QC was discussed and also emphasized. The absolute importance of measuring the dosing concentration on a routine basis before agents are administered to subjects was stressed during the discussion. The central role of Dr. Elston Seal was noted and comment was made that the HSD could benefit from centralized protocol management. The quality of the UNC IRB was noted, as well as the Board's involvement in review of the non-compliance and risk assessment. Finally, the Panel discussed issues related to training, mentoring, and establishment of a safety culture. Indeed, during the discussion, it was pointed out that maintenance of an on-going culture of conscience, compliance, and safety is "key" to protecting human subjects.

APPENDICES

Appendix A: Handouts

1. HSD Policy Manual (Volume #1)
2. HSD PM Manual (Volume #2)
3. HSD BDCM Manual (Volume #3)
4. NHEERL HSD Staff
5. Research Activities Involving Humans in the HSD
6. Suspended Studies List
7. EPA Quality System
8. PM Study IRB Minutes
9. BDCM Study IRB Minutes
10. BDCM Study Data Audit
11. PM & BDCM Study Participant Contact List.
12. Responses to Recent QA audit from July 24-25, 2002
13. Division Files for BDCM & PM Protocols
14. Forms & Format for IRB Renewal Notices
15. Letter from IRB in Response to EPA Violations 9/26/02

Appendix B: EPA Participants

PA ORD NCER Participants

Peter Preuss, Ph.D.
EPA Human Subject Research Review Official
Director, National Center for Environmental Research (NCER), ORD

Roger Cortesi, Ph.D.
Senior Science Advisor, ORD/NCER

EPA NHEERL Staff Participants

Larry Reiter, Ph.D.
Director

John Jones
Deputy Director for Management

Hal Zenick, Ph.D.
Associate Director for Health

John Vandenberg, Ph.D.
Director, Human Subject Division

Elston Seal, Ph.D.
NHEERL Human Rights Subject Official

Bob Devlin, Ph.D.
Branch Chief - Clinical Research Branch (CRB)

Rebecca Calderon, Ph.D.
Chief, Epidemiology & Biomarkers Branch

James Samet, Ph.D.
Acting Branch Chief during PM study violation, CRB Investigator

Steve Jackson
Facilities Oversight

Mike Ray
Quality Assurance Officer

Appendix C: EPA Site Review Team

Jorge G. Rangel, Jr.
Science Review Administrator
ORD/NCER/PRD

Joel Ann Todd
The Scientific Consulting Group, Inc.

Appendix D: University of North Carolina at Chapel Hill, School of Medicine, Committee on the Protection of the Rights of Human Subjects (IRB)

Daniel Nelson, Ph.D.
Director, Office of Human Research Studies

Ernest N. Kraybill, MD
Member & Former Chair

Stephen A. Bernard, MD
Chair

Appendix E: EPA NHEERL Principal Investigators

Theresa Leavens, Ph.D.
BDCM Study

Chong Kim, Ph.D.
PM Study



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

*Received
May 2 2005
Leathers*

Any action taken will investigate

MEMORANDUM

AUG 28 2002

OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Human Studies Evaluation and Corrective Action Plan

FROM: *Lawrence W. Reiter*
Lawrence W. Reiter, Ph.D.
Director, NHEERL (B305-01)

TO: Peter Preuss, Ph.D.
Human Subjects Research Review Official, ORD (8701R)

On August 19-21, 2002, a panel of four extramural experts met in Chapel Hill, NC to review the Human Studies Division (HSD) clinical policies and practices, and two incidents of protocol violations that occurred in the last year. At the conclusion of their site visit the panel members briefed key ORD, NHEERL and HSD managers and presented a report containing their observations and recommendations. We were very pleased by the thoroughness and quality of the panel review efforts and their report, and by the support provided by you and your staff members, Roger Cortesi and Jorge Rangel. We are in agreement with the panel recommendations, and we intend to implement immediately programs to address their recommendations and thereby furthering our efforts to assure the highest level of subject protection. Further, we are pleased that the panel chair concluded that implementation of proposed policies and procedures "will be entirely satisfactory and will meet current national standards", and that panel members concurred with our conclusion that no immediate or long-term adverse effects are expected from either protocol violation.

The panel members provided a number of important recommendations. We will immediately take steps to adopt and implement the new draft HSD policies and procedures, that address many of the recommendations provided by the panel with respect to procedural changes and dose assurances. We will immediately initiate other actions, such as mentoring and training programs, that will take some time to fully develop. Of key importance to such longer-term solutions is to create a climate of sustained attention, and to assure this we will schedule another external review focused on subject safety, within 3 years. The panel recommended development of new and streamlined procedures to ensure rapid reporting and evaluation of protocol violations, and for notification of affected subjects, that we will immediately work with your office to develop and implement. The panel strongly recommended that we develop comprehensive approaches to assure that errors in subject dosing do not occur. We agree that this is an absolutely essential requirement for our clinical studies, and no studies will be permitted without ensuring that policies and procedures, and quality assurance and quality control measures, are in place to characterize and assure the dose delivered to subjects is within prescribed limits. The panel made a number of suggestions and recommendations to further

strengthen our informed consent process and our relationship with the University of North Carolina Institutional Review Board, and we will work with the IRB to implement these procedures. The review panel also were very insightful and helpful in their suggestions and recommendations regarding the development of a research program culture focused on safety and compliance. We will immediately act to establish new mentoring efforts, to identify opportunities to use new tools and approaches to sustain vigilance, and clarify and extend our staff and management training. A fuller listing of the panel recommendations and our corrective actions are summarized in the attachment.

One notable item discussed with the panel is that in late April, 2003, the NHEERL (and HSD) Human Subjects Research Review Official, Dr. Elston Seal, intends to retire (he is a physician and commissioned officer in the Public Health Service). We have prepared position descriptions and are prepared to move forward with a personnel action to identify candidates and hire his replacement. The panel recommended that Dr. Seal's replacement play a central role in staff and management training, study oversight, and Institutional Review Board interactions, and, to accommodate this expanded role, additional administrative support should be considered to track and manage the complex process of protocol review and approval. We intend to address this need by evaluating technological as well as staff support, and for your information we already have had contact with strong candidates for this position. The review panel comments will be very helpful as we refine the role and responsibilities of this position, and we will take steps to ensure that we sustain strong support for Dr. Seal's replacement.

On June 21, 2002, upon discovery of a second unrecognized protocol violation in the previous year, I decided to suspend all of EPA's clinical research operations indefinitely. Based on information we provided, you supported this suspension and also linked any decision to lift the suspension on completion of an independent review of the protocol violations and the human studies policies and practices. The Human Subjects Review Panel report of August 21, 2002, provided sufficient information to generate the attached action plan. I believe that plan will ensure the appropriate process and safeguards by which to evaluate the current suspended work and future projects. With your concurrence, I will work with the HSD management to implement the action plan and determine, for each clinical study, whether or not to lift the research suspension.

Please let me know of your comments and concurrence regarding our corrective actions.

Attachment

cc: William Farland
Paul Gilman
John Jones
Henry L. Longest II
John Vandenberg
Hal Zenick

CORRECTIVE ACTION PLAN

The Human Subjects Review Panel was composed of four independent experts who each provided recommendations regarding policies, practices and programs to support clinical research at the Human Studies Division (HSD). In the table below the comments from the panel members have been organized and rephrased (in some instances) to improve clarity and eliminate redundancies. The proposed revised HSD Policies and Procedures that were provided to the Panel for comment will be reviewed and formally instituted by September 27, 2002. The draft NHEERL policies for human research also will be reviewed and formally instituted during 2002.

RECOMMENDATIONS	CORRECTIVE ACTIONS
<p><i>Reporting incidents and responsiveness</i></p> <ul style="list-style-type: none"> • ORD needs to develop a well-defined, streamlined process for when and to whom noncompliance should be reported • A process is needed for timely, efficient action relative to the protection of human subjects (in the event of noncompliance) • A streamlined process is needed to facilitate notification of subjects 	<ul style="list-style-type: none"> • HSD and ORD management (NHEERL and the Agency Human Subjects Research Review Official) will develop a formal streamlined process for noncompliance reporting, including identification and preparation of key managers whose concurrence is required. This will begin immediately and Dr. Elston Seal (HSD) will work with Roger Cortesi (NCER) and other individuals designated in NHEERL and ORD to develop this process.

RECOMMENDATIONS	CORRECTIVE ACTIONS
<p><i>Assuring Dose Delivered to Subjects</i></p> <ul style="list-style-type: none"> NHEERL must assure with absolute certainty the dose delivered to subjects, including independent verification of stability, homogeneity and concentrations of dosing solutions prior to subject exposure. 	<ul style="list-style-type: none"> The two recent HSD dosing violations occurred in studies where the principal investigator directly prepared and administered doses to subjects without prior independent verification of the dose to be delivered. This situation will not be allowed in the future. Rather, the proposed revised HSD policies and procedures (to be adopted by September 27) require involvement of the University of North Carolina Investigational Drug Pharmacy (or other expert consultant) and independent verification of dosing prior to any subject exposures. For those studies in which the HSD on-site contractor is responsible for delivery of pollutant dose to subjects (as is the case for nearly all HSD studies), HSD will continue to use present mechanisms which include substantial quality assurance and quality control measures with periodic independent evaluation throughout the duration of the study.

RECOMMENDATIONS	CORRECTIVE ACTIONS
<ul style="list-style-type: none"> • Identify (by the investigator) an acceptable range for delivered dose (or dosing solutions) for each protocol to indicate more precisely when an incorrect dosing event has occurred. • Measures of delivered dose should be included in all protocols, whether or not delivered dose is the parameter of concern. 	<ul style="list-style-type: none"> • All HSD protocols must specify an acceptable range of dosing solutions, based on factors such as instrument precision and toxicity of the pollutant. This requirement will be included in the module addressing clinical studies in the NHEERL policy document, to be completed in 2002. • HSD teams were instituted by HSD management (August 2002) to review protocol levels and measures regarding subject dosing. Further, these teams reviewed Standard Operating Procedures to assure they have been properly developed, peer reviewed, and received management sign-off, and the teams made recommendations. • Amendments to research protocols recommended by these teams (or the investigator) will be submitted for HSD management review and upon management concurrence will be submitted for approval by the IRB prior to any subject dosing. As defined in the proposed revised HSD policies, it is only after HSD management review (including the HSD/NHEERL Human Subjects Research Review Official) that amendments will be submitted to the IRB (this represents a policy change to assure amendments are reviewed to prevent "amendment creep" and assure management controls).
<ul style="list-style-type: none"> • Periodic re-review and audit of clinical studies to proactively identify and correct any problems, as well as improve study protocols 	<ul style="list-style-type: none"> • Final revised HSD policies to be instituted by September 27, 2002, will include a formalized review/audit process.

RECOMMENDATIONS	CORRECTIVE ACTIONS
<p><i>Institutional Review Board interactions including subject consent process</i></p> <ul style="list-style-type: none"> Consider establishment of a centralized Protocol Office 	<ul style="list-style-type: none"> HSD and NHEERL will evaluate staffing options and new technology support systems and select and implement option(s). This evaluation will begin immediately and the selection of an option(s) will be linked to the selection of a replacement, in 2003, of the HSD/NHEERL Human Subjects Research Review Official. In the interim, additional administrative support will be provided by HSD management to the HSD/NHEERL Human Subjects Research Review Official. Position description of HSD Human Subjects Research Review Official will be reviewed immediately, considering the panel comments, and revised as needed prior to announcement of vacancy.
<ul style="list-style-type: none"> Make EPA scientific review comments available to the IRB 	<ul style="list-style-type: none"> The proposed revised HSD policy will be revised to ensure EPA scientific review is completed before protocols are submitted to IRB.
<ul style="list-style-type: none"> Use a consent auditor to identify ways in which the consent process can be improved 	<ul style="list-style-type: none"> HSD management will identify and assign individuals to perform this role. With additional administrative support, Dr. Seal immediately will be assigned a leadership role in reviewing the consent process. In addition, HSD will train individuals and develop a program to routinely conduct audits.

RECOMMENDATIONS	CORRECTIVE ACTIONS
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

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May 2 2005
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Any action taken with investigators

MEMORANDUM

AUG 28 2002

OFFICE OF
RESEARCH AND DEVELOPMENT

SUBJECT: Human Studies Evaluation and Corrective Action Plan

FROM: *Lawrence W. Reiter*
Lawrence W. Reiter, Ph.D.
Director, NHEERL (B305-01)

TO: Peter Preuss, Ph.D.
Human Subjects Research Review Official, ORD (8701R)

On August 19-21, 2002, a panel of four extramural experts met in Chapel Hill, NC to review the Human Studies Division (HSD) clinical policies and practices, and two incidents of protocol violations that occurred in the last year. At the conclusion of their site visit the panel members briefed key ORD, NHEERL and HSD managers and presented a report containing their observations and recommendations. We were very pleased by the thoroughness and quality of the panel review efforts and their report, and by the support provided by you and your staff members, Roger Cortesi and Jorge Rangel. We are in agreement with the panel recommendations, and we intend to implement immediately programs to address their recommendations and thereby furthering our efforts to assure the highest level of subject protection. Further, we are pleased that the panel chair concluded that implementation of proposed policies and procedures "will be entirely satisfactory and will meet current national standards", and that panel members concurred with our conclusion that no immediate or long-term adverse effects are expected from either protocol violation.

The panel members provided a number of important recommendations. We will immediately take steps to adopt and implement the new draft HSD policies and procedures, that address many of the recommendations provided by the panel with respect to procedural changes and dose assurances. We will immediately initiate other actions, such as mentoring and training programs, that will take some time to fully develop. Of key importance to such longer-term solutions is to create a climate of sustained attention, and to assure this we will schedule another external review focused on subject safety, within 3 years. The panel recommended development of new and streamlined procedures to ensure rapid reporting and evaluation of protocol violations, and for notification of affected subjects, that we will immediately work with your office to develop and implement. The panel strongly recommended that we develop comprehensive approaches to assure that errors in subject dosing do not occur. We agree that this is an absolutely essential requirement for our clinical studies, and no studies will be permitted without ensuring that policies and procedures, and quality assurance and quality control measures, are in place to characterize and assure the dose delivered to subjects is within prescribed limits. The panel made a number of suggestions and recommendations to further

Attachment (2)

strengthen our informed consent process and our relationship with the University of North Carolina Institutional Review Board, and we will work with the IRB to implement these procedures. The review panel also were very insightful and helpful in their suggestions and recommendations regarding the development of a research program culture focused on safety and compliance. We will immediately act to establish new mentoring efforts, to identify opportunities to use new tools and approaches to sustain vigilance, and clarify and extend our staff and management training. A fuller listing of the panel recommendations and our corrective actions are summarized in the attachment.

One notable item discussed with the panel is that in late April, 2003, the NHEERL (and HSD) Human Subjects Research Review Official, Dr. Elston Seal, intends to retire (he is a physician and commissioned officer in the Public Health Service). We have prepared position descriptions and are prepared to move forward with a personnel action to identify candidates and hire his replacement. The panel recommended that Dr. Seal's replacement play a central role in staff and management training, study oversight, and Institutional Review Board interactions, and, to accomodate this expanded role, additional administrative support should be considered to track and manage the complex process of protocol review and approval. We intend to address this need by evaluating technological as well as staff support, and for your information we already have had contact with strong candidates for this position. The review panel comments will be very helpful as we refine the role and responsibilities of this position, and we will take steps to ensure that we sustain strong support for Dr. Seal's replacement.

On June 21, 2002, upon discovery of a second unrecognized protocol violation in the previous year, I decided to suspend all of EPA's clinical research operations indefinitely. Based on information we provided, you supported this suspension and also linked any decision to lift the suspension on completion of an independent review of the protocol violations and the human studies policies and practices. The Human Subjects Review Panel report of August 21, 2002, provided sufficient information to generate the attached action plan. I believe that plan will ensure the appropriate process and safeguards by which to evaluate the current suspended work and future projects. With your concurrence, I will work with the HSD management to implement the action plan and determine, for each clinical study, whether or not to lift the research suspension.

Please let me know of your comments and concurrence regarding our corrective actions.

Attachment

cc: William Farland
Paul Gilman
John Jones
Henry L. Longest II
John Vandenberg
Hal Zenick

CORRECTIVE ACTION PLAN

The Human Subjects Review Panel was composed of four independent experts who each provided recommendations regarding policies, practices and programs to support clinical research at the Human Studies Division (HSD). In the table below the comments from the panel members have been organized and rephrased (in some instances) to improve clarity and eliminate redundancies. The proposed revised HSD Policies and Procedures that were provided to the Panel for comment will be reviewed and formally instituted by September 27, 2002. The draft NHEERL policies for human research also will be reviewed and formally instituted during 2002.

RECOMMENDATIONS	CORRECTIVE ACTIONS
<p><i>Reporting incidents and responsiveness</i></p> <ul style="list-style-type: none"> • ORD needs to develop a well-defined, streamlined process for when and to whom noncompliance should be reported • A process is needed for timely, efficient action relative to the protection of human subjects (in the event of noncompliance) • A streamlined process is needed to facilitate notification of subjects 	<ul style="list-style-type: none"> • HSD and ORD management (NHEERL and the Agency Human Subjects Research Review Official) will develop a formal streamlined process for noncompliance reporting, including identification and preparation of key managers whose concurrence is required. This will begin immediately and Dr. Elston Seal (HSD) will work with Roger Cortesi (NCER) and other individuals designated in NHEERL and ORD to develop this process.

RECOMMENDATIONS	CORRECTIVE ACTIONS
<p><i>Assuring Dose Delivered to Subjects</i></p> <ul style="list-style-type: none"> NHEERL must assure with absolute certainty the dose delivered to subjects, including independent verification of stability, homogeneity and concentrations of dosing solutions prior to subject exposure. 	<ul style="list-style-type: none"> The two recent HSD dosing violations occurred in studies where the principal investigator directly prepared and administered doses to subjects without prior independent verification of the dose to be delivered. This situation will not be allowed in the future. Rather, the proposed revised HSD policies and procedures (to be adopted by September 27) require involvement of the University of North Carolina Investigational Drug Pharmacy (or other expert consultant) and independent verification of dosing prior to any subject exposures. For those studies in which the HSD on-site contractor is responsible for delivery of pollutant dose to subjects (as is the case for nearly all HSD studies), HSD will continue to use present mechanisms which include substantial quality assurance and quality control measures with periodic independent evaluation throughout the duration of the study.

RECOMMENDATIONS	CORRECTIVE ACTIONS
<ul style="list-style-type: none"> Identify (by the investigator) an acceptable range for delivered dose (or dosing solutions) for each protocol to indicate more precisely when an incorrect dosing event has occurred. Measures of delivered dose should be included in all protocols, whether or not delivered dose is the parameter of concern. 	<ul style="list-style-type: none"> All HSD protocols must specify an acceptable range of dosing solutions, based on factors such as instrument precision and toxicity of the pollutant. This requirement will be included in the module addressing clinical studies in the NHEERL policy document, to be completed in 2002. HSD teams were instituted by HSD management (August 2002) to review protocol levels and measures regarding subject dosing. Further, these teams reviewed Standard Operating Procedures to assure they have been properly developed, peer reviewed, and received management sign-off, and the teams made recommendations. Amendments to research protocols recommended by these teams (or the investigator) will be submitted for HSD management review and upon management concurrence will be submitted for approval by the IRB prior to any subject dosing. As defined in the proposed revised HSD policies, it is only after HSD management review (including the HSD/NHEERL Human Subjects Research Review Official) that amendments will be submitted to the IRB (this represents a policy change to assure amendments are reviewed to prevent "amendment creep" and assure management controls).
<ul style="list-style-type: none"> Periodic re-review and audit of clinical studies to proactively identify and correct any problems, as well as improve study protocols 	<ul style="list-style-type: none"> Final revised HSD policies to be instituted by September 27, 2002, will include a formalized review/audit process.

RECOMMENDATIONS	CORRECTIVE ACTIONS
<i>Institutional Review Board interactions including subject consent process</i>	
<ul style="list-style-type: none"> Consider establishment of a centralized Protocol Office 	<ul style="list-style-type: none"> HSD and NHEERL will evaluate staffing options and new technology support systems and select and implement option(s). This evaluation will begin immediately and the selection of an option(s) will be linked to the selection of a replacement, in 2003, of the HSD/NHEERL Human Subjects Research Review Official. In the interim, additional administrative support will be provided by HSD management to the HSD/NHEERL Human Subjects Research Review Official. Position description of HSD Human Subjects Research Review Official will be reviewed immediately, considering the panel comments, and revised as needed prior to announcement of vacancy.
<ul style="list-style-type: none"> Make EPA scientific review comments available to the IRB 	<ul style="list-style-type: none"> The proposed revised HSD policy will be revised to ensure EPA scientific review is completed before protocols are submitted to IRB.
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OFFICE OF THE INSPECTOR GENERAL
OFFICE OF INVESTIGATIONS

INTERVIEW OF REX PEGRAM

On May 19, 2005, SA DAVID L. COTNER, Special Investigations Unit, interviewed Dr. REX A. PEGRAM (919/541-0410), Research Biologist, EPA, Research Triangle Park (RTP), NC at the OIG offices located at RTP. Reporting agent properly identified himself to PEGRAM. The purpose of the interview was to support an investigation of allegations made to the Office of Special Counsel (OSC) by Dr. TED MARTONEN, alleging EPA researchers exposed subjects to at least one potentially dangerous compound in doses as much as one hundred times greater than those to which they consented and that EPA officials actively concealed the alleged wrongdoing of the EPA researcher.

PEGRAM stated he had worked for EPA since 1991 and had known MARTONEN since the same time. PEGRAM stated it had been over a month since he had last spoken to MARTONEN. PEGRAM stated he recalled a conversation he witnessed which involved Dr. MIKE DEVITO coming into a break room where MARTONEN was and stated there was an issue with Dr. CHONG KIM's di-2-ethylhexyl sebacate (sebacate) study in which subjects were exposed to sebacate in excess to what the subjects consented to receive. PEGRAM was unable to recall a specific time-frame of that conversation. PEGRAM did not believe it occurred prior to August 2001, as suggested by MARTONEN. PEGRAM recalled DEVITO stated he had just come from a meeting in Chapel Hill, NC with Dr. LINDA BIRNBAUM, then Acting Director of Human Studies Division (HSD), and that DEVITO stated KIM's study had over-exposed subjects to sebacate. Although PEGRAM was not clear of the time specific time-frame, he recalled BIRNBAUM was the Acting Director of HSD. PEGRAM was unable to recall that the conversation occurred prior to August 2001. (AGENT's NOTE: BIRNBAUM was the Acting Director of HSD from about February 2001 to about February 2002).

PEGRAM stated he would not have been the source of information to MARTONEN of the specifics of a meeting involving BIRNBAUM and the Human Subject Review Panel (HSRP) during 2002, as suggested by MARTONEN that PEGRAM told him BIRNBAUM glossed over KIM's study to HSRP. PEGRAM stated there was no way he would know what happened because he was not at those meetings. PEGRAM did not recall anyone telling him something similar, either.

Investigation Conducted on: May 19, 2005	Conducted at: Research Triangle Park, NC
Conducted by: SA David L. Cotner	OI File No: 2005-0002
Date Prepared: May 19, 2005	Prepared by: SA David L. Cotner <i>[Signature]</i>