USACHPPM

U.S. Army Center for Health Promotion and Preventive Medicine
(Provisional)

FINAL
FIELD STUDY NO. 75-23-YS50-94
HEALTH RISK ASSESSMENT OF CONSUMING DEER FROM
ABERDEEN PROVING GROUND, MARYLAND
MAY 1995

REPORT AND
APPENDICES A-D

HEALTH EFFECTS RESEARCH PROGRAM

U.S. ARMY CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE (Provisional)

The U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) lineage can be traced back over a half century to the Army Industrial Hygiene Laboratory which was established at the beginning of World War II under the direct jurisdiction of The Army Surgeon General. It was originally located at the Johns Hopkins School of Hygiene and Public Health with a staff of three and an annual budget not to exceed three thousand dollars. Its mission was to conduct occupational health surveys of Army-operated industrial plants, arsenals, and depots. These surveys were aimed at identifying and eliminating occupational health hazards within the Department of Defense' s (DOD) industrial production base and proved to be extremely beneficial to the Nation's war effort.

Most recently, the organization has been nationally and internationally known as the U.S. Army Environmental Hygiene Agency (AEHA) and is located on the Edgewood area of Aberdeen Proving Ground, Maryland. Its mission had been expanded to support the worldwide preventive medicine programs of the Army, DOD and other Federal agencies through consultations, supportive services, investigations and training.

On 1 August 1994, the organization was officially redesignated the U.S. Army Center for Health Promotion and Preventive Medicine and is affectionately referred to as the CHPPM. As always, our mission focus is centered upon the Army Imperatives so that we are optimizing soldier effectiveness by minimizing health risk. The CHPPM's mission is to provide worldwide scientific expertise and services in the areas of:

- Clinical and field preventive medicine
- Environmental and occupational health
- Health promotion and wellness
- Epidemiology and disease surveillance
- Related laboratory services

The Center's quest has always been one of customer satisfaction, technical excellence and continuous quality improvement. Our vision is to be a world-class center of excellence for enhancing military readiness by integrating health promotion and preventive medicine into America's Army. To achieve that end, CHPPM holds everfast to its core values which are steeped in our rich heritage:

- Integrity is our foundation
- Excellence is our standard
- Customer satisfaction is our focus
- Our people are our most valuable resource
- Continuous quality improvement is our pathway

Once again, the organization stands on the threshold of even greater challenges and responsibilities. The CHPPM structure has been reengineered to include General Officer leadership in order to support the Army of the future. The professional disciplines represented at the Center have been expanded to include a wide array of medical, scientific, engineering, and administrative support personnel.

As the CHPPM moves into the next century, we are an organization fiercely proud of our history, yet equally excited about the future. The Center is destined to continue its development as a world-class organization with expanded preventive health care services provided to the Army, DOD, other Federal agencies, the Nation, and the world community.

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Aberdeen Proving Ground (APG) is a United States Army installation located on the western banks of the upper Chesapeake Bay, Maryland. The APG has been in operation for over 75 years with primary mission of research, development, and testing of munitions and military vehicles. As a results of APG being on the National Priorities List, an installation-wide health risk assessment is currently underway. As part of this health risk assessment, all potential human exposure pathways are being investigated to include the food chain. Hunters harvest approximately 800 whitetail deer from APG annually. To assure public safety, a study was completed by the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) to identify any potential human health hazards associated with consumption of deer harvested from APG.

During the 1993 hunting season, scientists from USACHPPM collected 150 deer samples (muscle and liver) from hunters. These samples were analyzed for several explosives and breakdown

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19. products, polychlorinated biphenyls (PCBs), heavy metals, and organochlorine pesticides (DDT, DDD, DDE). For background and comparison purposes, deer were also sampled from areas off the installation within the state of Maryland. Data from the chemical analyses revealed no detectable levels of explosives, PCBs, or organochlorine pesticides. However, low concentrations of several heavy metals were identified in deer from both APG and off post. These values were compared statistically, but no consistent patterns or trends between the sites and metal tissue levels were seen.

To determine if these metal levels posed a hazard to consumers, a health risk assessment was completed. Actual consumption data obtained from a hunter's questionnaire was used to define exposure (eg. how much venison harvested from APG do the hunters and their families actually consume per year). Arsenic, cadmium, chromium, and mercury levels were evaluated using the U. S. Environmental Protection Agency (EPA) Guidance for Risk Assessment at Superfund Sites. Arsenic levels were also compared to established standards - Applicable or Relevant and Appropriate Requirements (ARARs). At the moment, there are no standard EPA methods to evaluate lead and nor ARARs for comparison. So lead levels were evaluated using a similar method used by the U.S. Food and Drug Administration (FDA) for lead in shellfish. A synopsis of the findings and associated uncertainties is presented below.

Following the standard EPA risk assessment methodology, cadmium, chromium, and mercury levels in APG deer posed no significant risk to consumers but initially, arsenic levels appeared to contribute the most to the potential risk. However, this risk may be overestimated because of the conservation assumptions and uncertainities associated with the toxicity values for arsenic. Also, most reported toxicity values are derived for the inorganic form of arsenic as opposed to the less toxic organic form; but the actual forms of arsenic in deer is unknown at this time. It has been reported in the literature that only 10% of the arsenic found in shellfish is in the inorganic form.

Due to the inherent uncertainties associated with arsenic, levels were also compared to establish standards or Applicable or Relevant and Appropriate Requirements (ARARs). Arsenic levels in deer were compared to FDA arsenic standards for tolerable residues exposures in beef and pork (0.5 mg/kg and 0.7 mg/kg respectively) associated with arsenic used as a feed additive and the use of arsenical pesticides. Again, most of theses values have been established for the inorganic form of arsenic. Levels in deer from APG and offpost sites were similar or slightly higher than these values. Additionally, calculated intake levels of arsenic by hunters eating deer from APG were compared to acceptable daily intake values for arsenic established by the World Health Organization (WHO). None of the arsenic intake values based on the 95% Upper Confidence Limits exceeded any of the WHO criteria.

Currently, there are no standard EPA methods available to evaluate lead in edible tissue. Therefore, the FDA method for evaluating lead in shellfish was applied in this study. Maximum lead levels of concern were based on exposure factors (EPA standards and hunter consumption data collected during the study) and on provisional tolerable total intake levels for general and sensitive populations (ie. adults, pregnant women, school age children, and children under 6 years). Lead levels in deer tissue were compared to these acceptable maximum levels. Overall, the lead levels in deer from both APG and offpost were within the acceptable safe limits.

Based on these data and considering the conservatism and uncertainty related to the current risk assessment process, the health risk associated with consuming meat for APG deer is no greater than that associated with consuming meat from offpost deer. Therefore, consumption of APG deer following the current practices identified in this report should not present an elevated human health hazard.

DEPARTMENT OF THE ARMY
U.S. ARMY CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE (PROVISIONAL)
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO ATTENTION OF MCHB-DL-HE

EXECUTIVE SUMMARY

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During the 1993 hunting season, scientists from USACHPPM collected 150 deer samples (muscle and liver) from hunters. These samples were analyzed for several explosives and breakdown products, polychlorinated biphenyls (PCBs), heavy metals, and organochlorine pesticides (DDT, DDD, DDE). For background and comparison purposes, deer were also sampled from areas off the installation within in the state of Maryland. Data from the chemical analyses revealed no detectable levels of explosives, PCBs, or organochlorine pesticides. However, low concentrations of several heavy metals were identified in deer from both APG and off post. These values were compared statistically, but no consistent patterns or trends between the sites and metal tissue levels were seen.

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I. INTRODUCTION.

A. Summary. As part of the installation-wide health risk assessment, all potential exposure pathways to contaminants are currently under investigation. This process includes investigating the potential pathway through the food chain in several game species.

B. General. Hunters harvest approximately 1,000 whitetail deer annually from APG. To assure public safety, a study was completed to determine body-burden levels in the resident deer population and to identify any potential human health hazards associated with consumption of these deer.

II. BACKGROUND

A. Installation Description. The Aberdeen Proving Ground was established in 1917 and historically has been used for research, development, and testing of chemical warfare agents and conventional munitions. The installation occupies approximately 32,400 hectares of relatively undeveloped coastal plain uplands, wetlands, and estuarine environments on the upper Chesapeake Bay in Maryland (see map 1).

B. Site History. As a result of historical testing and waste disposal practices and findings of some localized chemical contamination in the waters, sediments, and soils, APG has been placed on the National Priorities List (see reference 1). Known or suspected chemical contaminants include munitions and their breakdown products, solvents, pesticides, heavy metals, and polychlorinated biphenyls (PCBs) (see reference 1).

III. PURPOSE

A. Summary. As part of the investigative process, the U.S. Army Center of Health Promotion and Preventive Medicine (USACHPPM), formerly the U.S. Army Environmental Hygiene Agency (USAEHA), was tasked by the APG Directorate of Safety, Health, and Environment (DSHE) to determine if consuming resident deer posed a human health risk. This report contains a health risk assessment based on consuming deer harvested from APG and from other areas in Maryland. Also, included in this report are data from a small pilot study conducted in 1993.

B. Contaminants of Concern.

1. Selection of the Contaminants of Concern. Several criteria were used to select the chemicals for analysis. These criteria were as follows: a history or evidence of environmental contamination of a specific chemical, the toxicity of the chemical, the environmental fate of the chemical especially their persistence in the environment, and the lipophilic properties of a chemical (i.e., will the chemical bioaccumulate in the food chain). Polychlorinated biphenyls (PCBs), organochlorine pesticides (DDT, DDD, DDE), and mercury, were selected because they have been found on APG, are persistent in the environment, and tend to bioaccumulate through the foodchain. Lead, arsenic, chromium, and cadmium were selected because they have been detected in the soil, can concentrate in biologic tissue and can be toxic to both humans and animals. The explosives 2,4,6-TNT and its metabolites (1,3-DNB, 1,3,5-TNB, 2-A-4,6-DNT, and 4-A-2,6-DNT), RDX, HMX, 2,4-DNT, and 2,6-DNT were selected because of the limited information available concerning uptake and bioaccumulation in game species such as deer.

2. Other Contaminants of Concern. Although other chemical munitions such as the organophosphate compounds, mustard agent, lewisite, and white phosphorus have a history of past use at APG, they were not selected as chemicals of concern because the did not meet the selection criteria. These compounds rapidly degrade in the environment and are not lipophilic; therefore, they are not likely to bioaccumulate in the food chain. Also, these munitions have not been consistently detected in the soil; therefore, there probably is no complete pathway to deer.

C. Literature Review. Several studies of residue levels in whitetail deer exist in the literature. Most of these studies are associated with heavy metals, pesticides, and polychlorinated biphenyls. Only three studies exist in the literature that address the issue of whitetail exposed to military unique compounds. A summary of these studies is given below.

1. Explosives. According to the literature, military unique compounds typically are not found in wildlife. The three studies referenced showed that explosives were not detected in wildlife including deer exposed to high levels of explosives in soil from Army Ammunition Plants. Shugart, et.al. looked for residue levels of trinitrotoluene and nine metabolites in deer, quail, and rabbits from Alabama Army Ammunition Plant, Childerburg, Alabama. These compounds were not detected above the analytical detection limit of 0.2 mg/kg (see reference 5). Shugart et.al. also looked for 2,4-and 2,6-dinitrotoluene in deer from Badger Army Ammunition Plant, Baraboo, Wisconsin and again these compounds were not seen above the analytical detection limit of 0.1 mg/kg (see reference 6). Finally, USAEHA conducted an extensive study of whitetail deer from Joliet Army Ammunition Plant (JAAP), Joliet, Illinois. Various tissues were analyzed for trinitrotoluene including four metabolites, RDX, HMX, 2,4- and 2,6-dinitrotoluene. The detection limits ranged from 0.05 to 0.2 mg/kg. Although levels in the soil were high especially around the explosive manufacturing areas, none of these compounds were detected in the deer (see reference 3).

2. Metals. Several tissues serve as reservoirs for metal deposition. For example, arsenic tends to sequester in bone and hair, and cadmium in kidney. Some heavy metals can accumulate in edible tissue such as the case with mercury. Seasonal, sex, and age variations may have an impact on bioaccumulation of metals as noted in the literature, but these findings are inconsistent (see reference 4).

3. Organochlorine Pesticides. The organochlorine pesticides DDT, DDE, and DDD are no longer manufactured in the U.S.; however, due to a history of widespread use and persistence in the environment, they remain a potential threat to wildlife. Because of their bioconcentration properties, organochlorine pesticides represent one of the most serious problems in terms of biomagnification in the food chain. Generally, these pesticides bioaccumulate in adipose tissue (fat) of mammals (see reference 5), providing a potential route of exposure for humans.

4. Polychlorinated Biphenyls (PCBs). Like organochlorine pesticides, PCBs are persistent and ubiquitous to the environment. Bioaccumulation of PCBs in mammals is well known, also having an affinity for adipose tissue (see reference 6).

5. Health Risk Assessments. Several human health risk assessments have been published based on consumption of deer harvested from known or suspected contaminated sites. A human health risk assessment based on deer harvested from a site in New Jersey revealed that cadmium levels in liver from older deer posed a risk to consumers. A health advisory was issued recommending that consumers limit their intake of older deer from this site (see reference 13). Heavy metal data from the JAAP deer study was used to determine risk to consumers. It was determined that the risk of consuming deer from JAAP was minimal and no higher than the risk of consuming deer from offpost (see references 2 and 7). A health advisory was not recommended.

IV. MATERIALS AND METHODS

A. Sampling.

1. Determination of Sample Size. An attempt was made to select and group samples by different strata: site, sex, and age. Prior to the study, a sample size of 10 was determine to be adequate to detect a change of one standard deviation from background with a power of 80% (Type II error = 20%) and alpha = 0.05 (Type I error = 5 %).

2. Sampling Areas. Whitetail deer (n=149) were sampled during the 1993/94 hunting season, from November 1993 through January 1994. The deer harvested from APG were collected from several areas on the Aberdeen peninsula, the Edgewood peninsula, and Graces Quarters/Carroll Island. Deer were also sampled from an offpost site west of APG (Gun Powder State Park - Sweet Air Parcel). Detailed descriptions of these are in Appendix A. See maps 1 and 2 for locations of study sites.

During the prior year, tissues (ie. muscle, liver, kidney, and bone) from 17 whitetail deer were obtained from another concurrent deer study conducted by Combat Systems Test Activity. These deer were harvested from the Impact area on APG and from the Eastern Shore of Maryland (Still Pond Creek Area) during November 1992 through February 1993. See maps 1 and 2 for study locations. Residue data from this pilot project were used to develop the study design for the APG deer study in 1993/1994.

3. Sampling Period. Most of the sampling took place during the shot gun season: November 8 through December 11, 1993 (Aberdeen Areas); November 8 through November 28, 1993 (Edgewood Areas); and January 10 through January 12, 1994 (Gunpowder State Park). Several Edgewood deer were harvested in October 1993 during the APG bow season.

4. Permitting. Prior to the hunting season, hunters received written notification about participation in the deer study. This requirement was mandatory; failure to comply would have resulted in loss of hunting privileges at APG.

5. Stand Assignment. Each morning at the mandatory check stations, stands were assigned by a lottery system. The stands were preselected according to the location of the study areas. The hunter was required to participate in the study if he or she drew the preselected stand. Following the stand assignment, the participants were briefed on the details of the study including the hunter's role, a description of the anatomy of the whitetail deer specifying the location of the required organs, and a description of how to collect and store the tissue during field dressing.

6. Field Sampling Procedures. For this study, hunters from the selected study areas were required to harvest approximately 1 of pound liver and muscle, and two incisor teeth. Each morning at the check station, the hunters received a sampling kit containing a set of instructions, ice packs, aluminum foil, whirl-pack bags, and gloves. The hunters were directed to handle tissues cleanly, wrap the tissues in the aluminum foil, and store them in the pre-labeled whirl-pack bags. All distribution was supervised by the Study Director/USACHPPM personnel.

Deer from Grace's Quarters/Carroll Island were harvested by the Game Warden and DSHE personnel and processed by the Study Director. Deer from Gunpowder State Park (Sweet Air Parcel) were harvested by the Study Director. Deer from the pilot study were sampled by personnel from the Combat Systems Test Activity under the instruction of the USACHPPM by the Study Director.

7. Check Station Procedures. At the mandatory check stations (Aberdeen Area and Edgewood Area), each deer was logged in by the Study Director and/or USACHPPM personnel. Mandatory information was collected from the hunters including location of the kill (hunter/deer stand number), sex and weight of the deer. Also, a questionnaire was distributed to all hunters at the check station (see table 1). The bagged tissues (muscle and liver) were inspected by the Study Director/USACHPPM personnel, logged appropriately, and stored in a freezer until the following morning. Each morning, USACHPPM personnel transported the samples from the deer check stations to the USACHPPM Toxicology Division. The Study Director logged in the samples stored them at -32°C until analysis.

8. Quality Control (QC). Chain of Custody began at the check stations upon collection of tissues from hunters. Samples from each deer were visually inspected and logged in at the deer check station by USACHPPM personnel or the Study Director. The tissues were stored together in their respective bag and immediately frozen in a 0°C freezer at the check stations until transfer to the USACHPPM Toxicology Division by USACHPPM personnel where they were logged in

through the USACHPPM Laboratory Customer Services Division and stored at -32°C until analysis.

B. Residue Analysis.

1. Analytical Methodology.

(a) Quality Control. Muscle and liver samples were processed through the USACHPPM Laboratory Customer Services Division, assigned QC numbers and distributed to the various laboratories. All data were reported as a mg/kg wet weight basis. The analyses were performed by the USACHPPM Directorate of Laboratory Sciences following Good Laboratory Practices.

(b) Analytical Procedures.

(1) Explosives. The analysis for explosives was performed by the Special Analysis Branch of the Organic Environmental Chemistry Division using USAEHA-OECD Standard Operating Procedures (SOP) 51.4. The method involved extraction of a 2 gram tissue aliquot with acetonitrile followed by a solid- phase extraction cleanup and concentration. The extracts were analyzed using both high performance liquid chromatography with ultra-violet detection and gas chromatography with mass selective detection. See Appendix B for a detailed standard operating procedure.

(2) Metals. Metals were analyzed by the Metals Analysis Branch of the Radiological and Inorganic Chemistry Division using USAEHA-RICD SOP-MDP-23 and MAB-MDP-10. A 2 gram aliquot of frozen homogenized tissue was digested in nitric acid and hydrogen peroxide. The digested portion was then analyzed using one of the following: Inductively Coupled Plasma (ICP), Graphite Furnace Atomic Absorbance, or ICP-Atomic Emission Mass Spectrometry for arsenic, cadmium, chromium, and lead. For mercury analysis, a 0.5 gram sample of the initial aliquot was digested in nitric acid using a Paar Bomb procedure. This aliquot was then processed using dilute potassium permanganate-potassium persulfate solutions and oxidized at 95 °C for 2 hours. Mercury in the digested sample was reduced with stannous chloride to elemental mercury and measured by the Conventional Cold Vapor Atomic Absorption Spectroscopy technique. See Appendix C for a detailed standard operating procedure.

(3) Organochlorine Pesticides and PCBs. Both organochlorine pesticides and PCBs analyses were performed by the Pesticide Analysis Branch of the Organic Environmental Division using SOP 37.1 with approved modifications/deviations and contained in the SOP in Appendix D. Twenty five - 50 grams of ground muscle tissue or liver tissue, mixed with sodium sulfate, was extracted in a high speed explosion proof blender jar with successive portions of petroleum ether (PE). The combined extracts were passed through a drying column, concentrated to 10 ml on a water bath or a Zymark TurboVap concentrator and transferred to a 50 ml beaker. All solvent was removed, and the resulting fat weight was determined. Four grams or less of the fat were dissolved in a 1:1 mixture of methylene chloride:cyclohexane if Zymark robotic Gel Permeation

(GPC) was employed. If acetonitrile partitioning was used as a cleanup step, 2 grams or less of the fat were dissolved in PE. The pesticides/PCB residues were then partitioned from the PE solution into acetonitrile. The acetonitrile extract was diluted with NaCl-containing water and the residues were extracted back into PE. The PE extract was dried, concentrated to 4-5 ml on a water bath or TurboVap concentrator. The GPC extract was concentrated using either of the methods mentioned above; however, a solvent transfer into PE or hexane was also performed. Both extract procedures were cleaned and fractionated further using a florisil cleanup column and the residues eluted with a mixture of ethyl ether/PE. The florisil eluate fraction was concentrated, a solvent transfer into iso-octane was performed, and it was then analyzed by electron-capture gas chromatography.

c. Project Reporting Limits (PRLs). Explosives, organochlorine pesticides, and PCBs residues are reported as PRLs. These values represent the lowest value that can be routinely and reliably detected in the specific matrix. Metal residue data are reported as the Detection Limits (DLs). These values represent the lowest amount residue that can be distinguished from the normal "noise" of an analytical instrument or method. The chemicals of concern, the PRLs, and the DLs are listed in Table 2.

V. RESULTS

A. Summary. This section contains summaries of the field data and analytical results. Analytical data from the pilot study are also included. The data are organized in tables at the end of this report.

B. Field Data. These data represent deer identification, location of kill, sex, weight, and age if available (see Table 3). Age estimation was determined by histologic examination of the incisor tooth cementum (Matson's Inc.). Tooth data from the Edgewood deer are not available at this time. The sample size for the APG deer study was 149 deer (129 from APG, 20 from Gunpowder State Park). The gender distribution is as follows: male = 72 (62 from APG, 10 from Gunpowder State Park) and female = 77 (67 from APG, 10 from Gunpowder State Park). The average dressed weight for the APG deer was 81 pounds and for Gunpowder State Park deer was 72 pounds.

The only field data collected during the APG pilot deer study were location of kill and gender. The sample size for APG was 12 (all females) and for the Eastern Shore was 5 (3 males and 2 females).

C. Residue Data. The following is a summary of analytical data. The corresponding tables listed can be found at the end of this report.

1. Explosives (Table 4). No explosive analytes or breakdown products were detected in any sample.

2. Organochlorine Pesticides and PCBs (Table 4). No organochlorine pesticides or PCBs were detected in any sample.

3. Metals Data. The means and standard deviations can be found in Tables 5a, 5b, 5c, and 5d. Low concentrations of metals were detected in deer from APG and offpost. Raw data for the 1993/94 APG deer study are shown in Appendix B and shaded values represent those samples falling below the detection limits. Half of the detection limit was used in the statistical analysis.

(a) Statistical Evaluation. Metal data from the 1993/94 study were evaluated statistically to determine if inferences could be made between levels of metals and site, gender, and/or age. Data from the pilot study was not considered in this analysis because the study was conducted during the previous hunting season. All liver and muscle data were tested for normality using PROC UNIVARIATE in SAS. Logarithm and square root transformations of the data were also tested for normality. The data and the transformed data were not normally distributed. Therefore the data was analyzed using both parametric and nonparametric, rank transformation, approaches. The results were reported as means with standard deviations for ease of interpretation. A two-way analysis of variance (ANOVA) comparing site and gender was performed. Site and sex interactions were seen in several instances, but they were inconsistent. Since there were no consistent patterns between site and metals levels, the differences were considered biologically insignificant. Differences in metal concentrations among deer from all sample sites were compared using a one-way ANOVA and a Newman Keuls post-hoc test. In all cases, a $p < 0.05$ was considered significant. Several samples (muscle - # 91 arsenic and # 70 lead and liver - #34 for lead) were reanalyzed due to statistical nonconformity and these data are included in the statistical analysis. See Appendix B for a complete statistical description.

(b) The means, standard deviations, and ranges are listed in tables 5a (muscle) and 5b (liver). Statistically, significant differences between sites are denoted by footnotes. Generally, slight differences were seen with levels of arsenic in muscle and liver and cadmium in liver.

VI. DISCUSSION AND HEALTH RISK ASSESSMENT.

A. Summary. Low concentrations of some heavy metals were identified in muscle and liver from deer harvested from APG and offpost. Currently, there are no standards or acceptable residue levels in deer for these metals. Therefore, to determine if these levels pose a potential risk to consumers, a human health risk assessment was completed. The process followed the standard U.S. Environmental Protection Agency (EPA) Risk Assessment Methodology for Superfund Sites assuming conservative exposure scenarios. However due to the lack of information and uncertainties associated with the toxicity and actual exposure to arsenic and lead from deer meat, additional methods to estimate risk were applied. The following is a detailed description of these risk assessment processes.

B. Health Risk Assessment Process. Risk Assessment as defined by the EPA is the "the characterization of the potential adverse effects of human exposures to environmental hazards," (see reference 8). Risk assessment is an estimate of the probability that an adverse effect will occur do to a specific exposure scenario. The process of risk assessment consists of several elements: an exposure assessment, a toxicity assessment, and a risk characterization. See

Appendix C for a detailed description of this process. Levels of arsenic, cadmium, chromium, and mercury were evaluated using the EPA methodology. Arsenic was additionally characterized using Applicable or Relevant and Appropriate Requirements (ARARs). Lead was evaluated using the U.S. Food and Drug Administration (FDA) model for shellfish.

1. Exposure Assessment. An exposure assessment attempts to quantify the adult human exposure to a chemical contaminant. Exposure assessments identify several exposure factors: the population at risk and the magnitude, frequency, duration, and route of exposure. Typically, exposure factors are derived for the worst case scenario. For example, the assumed duration of a particular exposure to a specific contaminant is 30 years for carcinogenic effects. Also in this case, it was assumed that a specific contaminant detected in the deer meat was 100% available for gastric absorption. Information was compiled from field data and the Hunter's Questionnaire (table 1) to additionally quantify magnitude and frequency of exposure to include average deer weight (from which the amount of edible meat is estimated), average number of deer harvested from APG per year by each hunter, and the average number of household members that consume APG deer. Also from the questionnaire, only 19% of the hunters eat deer liver and even fewer consume other organs. So the risk assessment was based on consuming only muscle and liver. Exposure assessments describe the human exposures in terms of dosage in milligrams of substance per mass of body weight over time. The expressions below were used to calculate intake dosages:

Intake: A measure of exposure expressed as mass of a substance contacted per unit body weight per unit time.

$$\textbf{INTAKE(mg/kg-d)} = \frac{\textbf{CF x IR x FI x EF x ED}}{\textbf{BW x AT}}$$

CF = concentration in tissue (mg/kg). . . . . 95% UCL (mg/kg)
IR = ingestion rate (kg/meal) USEPA . . . . . 0.28(kg/meal)
FI = fraction ingested from contaminant source (unitless). . . 1
EF = exposure frequency (meals/year)
meat. . . . . 33 (meals/yr)
liver. . . . . 4 (meals/yr)
ED = exposure duration (years) 90% UCL. . . . . 30 years
BW = body weight (kg) average adult. . . . . 70 kg
AT = averaging time (days)
noncarcinogenic effects. . . . . ED x 365(d/yr)
carcinogenic effects. . . . . 70 yrs x 365(d/yr)

(a) **Facts and Assumptions.** Values for the above variables were derived in two ways. In order to obtain a single intake value for each contaminant of concern for use in the risk calculation, an attempt was made to develop a Reasonable Maximum Exposure (RME) scenario. For this, maximum estimates of the variables were derived based on the following data:

(1) In 1993/94, the average dressed weight of deer harvested from APG was 81 lb (36.8 kg).

(2) The average number of deer harvested per hunter per year was 2.1; so 2 was the value used in the intake calculation. This information was derived from the hunter's questionnaire; see table 1.

(3) Generally, about half of the dressed weight of the deer is available for meat consumption; therefore, in this case 18.4 kg. was the yield. Also, approximately 5 pound (2.3 kg) of liver is available for consumption.

(4) The ingestion rate of 0.28 kg/meal was taken from the USEPA Guidance for beef (see reference 8). This value and the amount of meat and liver available were used to determine the consumption frequency.

(5) A total of 66 meals/deer muscle and 8 meals/deer liver were available for consumption.

(6) From the Hunter's Questionnaire, hunters share the meat among a family of four. This value was then multiplied by two (average number deer per season) yielding an exposure frequency of 33 meals per year for deer meat and 4 meals per person per year for deer liver.

2. Toxicity Assessment. The purpose of the toxicity assessment is to weigh the evidence and evaluate the potential for adverse effects to an individual from exposure to a particular contaminant. Also, the toxicity assessment may provide, where possible, an estimate of the relationship between the extent of exposure to a contaminant and the increased likelihood and/or severity of adverse effects (see reference 8). Generally, toxicity assessments are accomplished in two steps: hazard identification and dose-response assessment. The following is a description of this process.

(a) Hazard Identification is the process of determining whether exposure to a chemical can cause an increase in the incidence of a particular adverse effect and whether the adverse effects are likely to occur in humans.

(b) Dose-Response Evaluation is the process of quantitatively evaluating toxicity information and characterizing the relationship between the dose of a contaminant administered or received and the incidence of adverse health effects in the exposed population. From this relationship, toxicity values are derived that can be used to estimate the likelihood of that an adverse effect will occur at different exposure levels (see reference 8). The toxicity values used in this risk assessment are listed in table 2.

(1) Information generated from the dose-response evaluation include toxicity values for carcinogenic and noncarcinogenic effects. For noncarcinogenic effects, a **reference dose (RfD)** is determined and represents an estimate of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious

effects during a lifetime (see reference 8). However, these values are not exact, and the associated uncertainty may span perhaps an order of magnitude. The RfD values for each compound are listed in table 2. Note that the more conservative RfD for chromium (Cr 6) was used.

(2) For carcinogenic effects, a **slope factor (SF)** is used to represent an upper bound probability of developing cancer per unit of intake. It is derived from a mathematical extrapolation of toxicity dose response data (see reference 8).

(3) Also, the EPA classifies carcinogens qualitatively by the extent to which the available data indicate that an agent is a human carcinogen; this is the **weight of evidence (WOE)**. The weight of evidence categories are as follows: A = human carcinogen; B1 = probable human carcinogen, limited human data are available; B2 = probable human carcinogen, sufficient evidence in animals and inadequate or no evidence in human; C = possible human carcinogen; D = not classifiable as to human carcinogenicity; E = evidence of non-carcinogenicity for humans (see reference 8). The WOE values for each compound are listed in table 2.

(4) A toxicity profile for each of the contaminants of concern can be found in Appendix D. The toxicology databases for the metals are fairly complete; however, arsenic and lead require additional consideration.

(5) The EPA has derived a RfD for arsenic (inorganic arsenic) primarily based on a study by Tseng et.al. (see reference 16). This study showed an increased incidence of blackfoot disease, hyperpigmentation, and keratosis in a Taiwanese population exposed to arsenic in drinking water. However, the EPA states that there are several shortcomings associated with this study. For example, the Tseng studies did not consider the potential exposure from food or other sources. In addition, these findings were not substantiated following a similar study in the U.S. where a population was exposed to arsenic in the drinking water. Although the RfD was based on human epidemiological studies, the EPA only accepts the RfD with medium confidence and they suggest that the RfD for arsenic may vary by perhaps an order of magnitude (see reference 9). The RfD for arsenic is still under investigation by the EPA, and they suggest that risk managers should be flexible when formulating regulatory decisions (see reference 9).

(6) Similar uncertainty exists with interpretation of the cancer risk associated with arsenic (inorganic arsenic). Arsenic has been reported to cause lung and skin cancer in humans. Lung cancer has occurred in smelter and pesticide manufacture workers through the inhalation of inorganic arsenic. Again, Tseng et.al. (see reference 17) reported an increased prevalence of skin cancers in humans exposed to inorganic arsenic in drinking water. Based on these findings, the EPA has assigned a weight of evidence classification A to inorganic arsenic (see reference 9). However, the EPA has not derived a caner potency factor (slope factor) for arsenic but they have assigned it a unit risk factor of 5E-5/ug/L based on the Tseng et.al. study (see reference 9). According to the Integrated Risk Information System database (IRIS), a recent memorandum by the Administrator of the EPA stated that "in reaching a risk management decision in a specific situation, risk managers must recognize and consider the qualities and uncertainties of risk

estimates." The uncertainties associated with ingested inorganic arsenic are such that estimates could be modified downwards as much as an order of magnitude (less risk of cancer), relative to risk estimates associated with most other carcinogens (see reference 9).

(7) Considering the above information and other relevant uncertainties associated with what form of arsenic is actually in deer meat, risks due to arsenic levels in deer were determined using additional methodologies comparing levels to Appropriate and Relevant Applicable Requirements. See section 3(2) for risk characterization.

(8) By comparison to most other environmental contaminants, the degree of uncertainty about the health effects of lead is quite low. It appears that some of the effects (eg. changes in the blood enzyme levels and neurobehavioral development of children) may occur at blood levels so low as to be essentially without a threshold. Therefore, the EPA has considered it inappropriate to develop an RfD for inorganic lead (see reference 9). Also, quantifying the potential risk of cancer due to lead exposure involves many uncertainties some of which may be unique to lead. Age, health, nutritional state, body burden, and exposure duration influence the absorption, release, and excretion of lead. In addition, current knowledge of lead pharmacokinetics indicates that an estimate derived by standard procedures would not truly describe the potential risk. Thus, the EPA recommends that a numerical estimate such as a slope factor not be used (see reference 9). For this study, the lead levels were compared to the provisional tolerable total intake levels (PTTIL) used by the FDA for lead in shellfish, (see section 3(3) risk characterization of lead).

3. Risk Characterization. Risk Characterization is the final step of the health risk assessment process and involves summarizing and integrating the toxicity and exposure assessments into quantitative and qualitative expressions of risk. Again, it is only an estimate of the probability that an adverse effect will occur due to an exposure to one or more specific contaminants. To characterize potential noncarcinogenic effects, comparisons are made between projected intake of substances and toxicity values. To characterize potential carcinogenic effects, probabilities that an individual will develop cancer over a lifetime of exposure are estimated from projected intake and chemical-specific dose-response information. Major assumptions, scientific judgements, and to the extent possible, estimates of the uncertainties embodied in the assessment are also considered (see reference 8).

(a) **Non-Carcinogenic Risk**.

(1) According to the EPA methodology, noncarcinogenic risks are evaluated by comparing the intake estimates from the exposures assessment to the RfD (see reference 8). This comparison is called a **hazard quotient (HQ)**. For mixtures of compounds found in different environmental media, the assumption was made that chemicals interact in an additive fashion (see reference 8). The individual HQs are typically added to yield an overall **hazard index (HI)** (see reference 8). The HQ's and HI's represent comparisons of estimated intake levels to safe intake levels; however, they do not show a probability of developing an adverse effect. The HI scores of less than one indicate that exposure to all contaminants in a mixture falls within the safe level (see reference 8). Any HI value greater than one is a potential cause for concern; however, the levels

of concern are proportional to increasing HIs. In this instance, contaminants may be re-evaluated and grouped by target organ toxicity; HI scores could be re-calculated on this basis.

(2) The noncarcinogenic risks for both the APG deer study and the pilot study were based on the upper 95% confidence limit of the arithmetic mean for each metal; this follows the EPA methodology and results in a more conservative number. The HI values for both studies are shown in tables 6a, 6b, and 6c, and the derivatives for these calculations are shown in table 8. All of the HI scores for ingestion of liver from all areas are less than one. The HI scores for muscle did slightly exceed one for several sites including the Eastern Shore with the highest HI value at 1.8.

(3) Arsenic levels represent 67% to 90% of the risk. However, the RfD values assigned by the EPA refer to the inorganic form of arsenic primarily in drinking water. Arsenic exists in the environment naturally and anthropogenically (man-made). Arsenic is widely distributed in the environment especially in industrial regions and areas of large application of arsenical herbicides (see reference 12). Some researchers claim that low levels of arsenic may be an essential requirement for reproduction and growth for both plants and animals and this fact has lead farmers to add arsenic to livestock feed (see reference 12). Arsenic is encountered in both the inorganic and organic form. Two major metabolic pathways for arsenic have been identified in humans and animals: oxidation-reduction reactions for the interconversion of arsenates and arsinites in the body, and methylation reactions that ultimately convert these compounds to monomethylarsine and dimethylarsine as metabolic products (see reference 13). A number of studies have confirmed that the methyl derivatives of arsenic appear to be less toxic than the parent compound, and since methylation tends to reduce the retention of inorganic arsenic in tissues, the methylation process is the "detoxification" mechanism (see reference 12).

(4) To date, there is no information concerning what form of arsenic actually occurs in deer meat. In fact, limited data exists concerning the form of arsenic in beef and pork. An unpublished study found in an EPA Risk Assessment Forum document stated that the arsenic in beef and pork is up to 75% inorganic (see reference 14). But well published studies of fish and shellfish have revealed that arsenic occurs predominantly in the organic form (see reference 10). Available information indicates that inorganic arsenic levels will on the average account for less than 10% of the arsenic in shellfish (see reference 10). At any rate, inorganic arsenic doesn't seem to occur in biological tissue at 100%, thus the potential risk estimated in this study is probably conservative.

(5) Most of the ARARs for comparison were derived for inorganic arsenic associated with food additives and pesticides. For example, the FDA has set tolerance levels for total arsenic residues in meat associated with feed additives. For swine and poultry meat products, an acceptable level in edible tissue of 0.5 ug/g has been established (21 CFR 556.60). Also, the FDA has set tolerances for residues of arsenic containing pesticides. For beef and horse meat, fat and by-products, the acceptable level is 0.7 mg/kg for both dimethylarsinic acid (21 CFR 180.311) and for sodium arsenite (21 CFR 180.235) (see reference 15). The highest UCL arsenic values were seen in deer from the Impact area (0.858 mg/kg for the APG study and 0.966 mg/kg for the pilot study) and from the Eastern Shore (0.979 mg/kg). Arsenic levels were also compared to

the World Health Organization's tolerable daily intake of inorganic arsenic (2 ug/kg body weight/day) (see reference 9).

(6) For comparison purposes, these values were converted to dosages in mg/kg-d. Figure 1 below compares estimated intake values associated with arsenic in deer to the converted intake values derived from ARARs. All intake values associated with arsenic in deer fell below the values associated with the ARARs. Although some of the arsenic levels in deer exceeded the RfD and resulted in HIs values above one, these levels did not exceed other well established regulatory values for arsenic.

FIGURE 1: ARSENIC INTAKE FROM APG DEER vs. ARARs

Site	UCL (mg/kg)	Intake (mg/kg-d)
1	0.712	2.57E-4
2	0.858	3.10E-4
3	0.763	2.76E-4
4	0.723	2.61E-4
5	0.821	2.97E-4
6	0.463	1.67E-4
7	0.746	2.70E-4
8	0.434	1.57E-4
APG	0.966	3.49E-4
ES	0.979	3.54E-4

ARARs	Standards	Intake (mg/kg-d)
WHO	2 ug/kg-d	2.00E-3
FDA	0.5 ug/g (swine, poultry, meat edible tissue)	
	0.7 ug/g (beef, horse meat, by-products)	

APG = Pilot Study APG area
ES = Pilot Study Eastern Shore area
UCL = 95% Upper Confidence Limit $= \bar{x} + 1.96(\text{std dev}/\sqrt{n})$

(7) Finally, the arsenic levels were compared to background concentrations of wildlife found in the literature review. The National Academy of Sciences has reported background concentrations in living organisms are usually below 1 mg/kg fresh weight in terrestrial flora and fauna, birds, and freshwater biota (see reference 12).

(8) Currently, the EPA has not assigned an oral RfD or a slope factor for lead. Consequently, quantifying the risk associated with lead in deer tissue could not be accomplished using the standard EPA risk assessment methodology. Currently, no standards or ARARs have been established for lead in deer or beef. Lead levels were instead compared to PTTILs used by the FDA for lead in shellfish (see reference 11). The PTTILs were developed using information of the lowest levels of lead exposures associated with adverse effects (eg. neurobehavioral and cognitive development). Figure 2 below shows the recommended PTTILs. The values are as follows: 6 ug/day for children up to the age of 6 years, 15 ug/day for children 7 and older, 25 ug/day for pregnant women and 75 ug/day for adults (see reference 11).

(9) By comparing the PTTILs with the daily intake of deer for each population, acceptable lead levels in deer tissue were established. Daily intakes of beef for each population were derived from published values by the EPA and the U.S Department of Agriculture (USDA) (see references 8 and 18). The 95% Upper Confidence Limits for lead in muscle ranged from 0.145 mg/kg (Bombing area) to 1.04 mg/kg (Spesutie Island area). The 95% Upper Confidence Limits for lead in liver ranged from 0.0130 mg/kg (Eastern Shore) to 1.13 mg/kg (Spesutie Island). Only deer muscle from Spesutie Island exceeded the maximum acceptable lead levels for children under 7 years of age and pregnant women. The findings from the remaining sites were below the maximum acceptable lead levels for all of the age and gender groups.

FIGURE 2:

Provisional Tolerable Total Intake Levels (PTTIL)

$$\text{Total Lead Levels of Concern (ug/g)} = \frac{\text{PTTIL of Lead (ug Pb/day)}}{\text{Daily Intake of Deer (g/day)}}$$

1. **intake values of amount beef/meal**
   - **adults = 280 g/meal (EPA)**
   - **children < 7 years = 72 g/meal (USDA)**
   - **children > 7 years = 109 g/meal (USDA)**

2. **daily intake of deer muscle (33 meals/year)**
   - **adult = 25.3 g/day**
   - **children < 7 years = 6.51 g/day**
   - **children > 7 years = 9.85 g/day**

3. **daily intake deer liver (4 meals/year)**
   - **adult = 3.07 g/day**
   - **children < 7 years = 0.789 g/day**
   - **children > 7 years = 1.19 g/day**

4. **PTTIL for various population groups:**

Maximum Acceptable Lead Levels

Population	PTTIL (ug Pb/day)	Muscle (mg/kg)	Liver (mg/kg)
Children 0-6	6	0.922	7.60
Children 7 and over	15	1.52	12.6
Pregnant Women	25	0.988	8.14
Adults	75	2.96	24.43

5. **Lead Levels in Deer from APG and Offpost:**

Site	Muscle UCL (mg/kg)	Liver UCL (mg/kg)
1	1.04	1.13
2	0.369	0.153
3	0.145	0.250
4	0.189	0.134
5	0.659	0.158
6	0.469	0.464
7	0.595	0.164
8	0.443	0.238
APG	0.867	0.138
ES	0.424	0.0130

APG = Pilot Study APG area
ES = Pilot Study Eastern Shore area
UCL = 95% Upper Confidence Limit $= \bar{x} + 1.96(\text{std dev}/\sqrt{n})$

(b) **Carcinogenic Risk**. According to the EPA methodology, carcinogenic risks can be estimated by multiplying the INTAKE factor derived from the exposure assessment by the carcinogenic SLOPE FACTOR. The cancer risk represents an upper bound estimate of developing cancer as a result of the exposure in question. The EPA has established a range of acceptable cancer risk above the background incidence of cancer (1 person in 4) to be between 1E-4 (1 excess incidence in 10,000 people) to 1E-6 (1 excess incidence in 1,000,000 people) (see reference 8).

(1) For this analysis, only arsenic could be evaluated for cancer risks. Cadmium and chromium are carcinogenic but only by inhalation (see reference 9). Mercury has not shown to be carcinogenic; and although lead has been classified as a B2 carcinogen, the EPA has not given it a cancer potency factor (slope factor) because of the unique uncertainties associated with age, health, nutritional status, and exposure duration (see reference 9). Cancer risks for the APG sites and the reference sites are shown in tables 7a and 7b, and the derivatives for these calculations are shown in table 8.

(2) Inorganic arsenic is a human carcinogen based on studies of increased lung cancer in populations exposed through inhalation and on increased skin cancer in populations exposed through drinking water (see reference 9). Currently, no slope factor has been assigned by the EPA, but a unit risk concentration for inorganic arsenic in drinking water is available (5.05E-5 ug/L) (see reference 9). The unit risk is an estimate of carcinogenic risk at a water concentration of 1 ug/L. Based on this value, a slope factor of 1.75E+00 was derived yielding estimated cancer risks ranging from 1E-4 to 2E-4 for the APG study and up to 3E-4 for the pilot study. Cancer risks were similar among all sites including the offpost sites (Gunpowder State Park and Eastern Shore).

(3) Considering the conservative assumptions and the uncertainties associated with the actual form of arsenic in deer meat, the toxicity values assigned by the EPA (the SF may be overestimated by an order of magnitude), the bioavailability of arsenic (compared to water), and the exposure duration (33 meals/year for 30 years), these risk estimates may be unrealistic and overestimated. In all likelihood, actual risks are probably lower.

4. Uncertainty Analysis. The process of quantifying potential health risks resulting from exposures to environmental contaminants has been in use for a number of years and the techniques are continually being re-defined. Despite major advances in this area, there are still many uncertainties in both exposure assessment and the quantitative risk assessment. Also as previously mentioned, there is great uncertainty associated with arsenic.

(a) At this time, there is much conservatism built into the actual risk assessment methodology. Risk assessment is an estimate of a probability based on many assumptions of exposure and on toxicity values extrapolated typically from laboratory animals or on sparse human epidemiology studies. Noncarcinogenic risks are derived by comparing safe levels of a chemical to the actual exposure dose. Uncertainty factors from 1x to 10,000x are applied to extrapolate safe doses for humans. Although the RfD for arsenic was derived from human

epidemiological studies, the EPA recommends that risk managers be flexible with decisions based on arsenic levels because this value may vary by an order of magnitude. As for the cancer potential of arsenic, the EPA suggests that the estimates could be modified downwards as much as an order of magnitude (see reference 9).

(b) Currently, there is no information concerning the type or form of arsenic in deer tissue. Noncancer and cancer risks for arsenic were determined based on 100% inorganic arsenic. Several studies have shown that arsenic can occur in the inorganic form ranging from 10% in fish and shellfish to 75% in beef and pork (see ref. 14). Therefore, some if not most of the arsenic occurs in the less toxic organic form in biological tissues. And as a result, the estimated risks derived by this study may be too conservative.

(c) Lead could not be evaluated by the standard EPA risk assessment process. The EPA has not assigned a RfD or a slope factor to lead and acceptable FDA levels in deer or beef are not available at this time. So lead was evaluated using similar methods established by the FDA for shellfish comparing lead levels to PTTILs. The uncertainty is primarily associated with exposure estimates. Actual exposure may be overestimated especially for children.

VII. SUMMARY.

A. During the 1993/94 hunting season, scientists from USACHPPM collected samples of deer muscle and liver from hunters for analysis of several explosives, PCBs, metals, and pesticides. For comparison purposes, deer were also sampled from two off-post sites in Maryland. Data from the chemical analyses revealed no detectable levels of explosives, PCBs, or organochlorine pesticides (DDT, DDD, DDE). Low concentrations of several heavy metals were identified in muscle and liver of deer sampled from APG and from the off-post sites in Maryland. There were no consistent patterns or trends between sites and metal tissue levels.

B. Tissue levels of metals (arsenic, cadmium, chromium, and mercury) were evaluated for risk to consumers following the EPA Guidance for Risk Assessment at Superfund Sites (see reference 8). Consumption data from a Hunter's Questionnaire were used to determine actual exposure information. Arsenic appeared to be contributing most to the risk of consuming deer harvested from both APG and off-post sites; however, using the conservative exposure assumptions suggested by the EPA guidance, and assuming that the form of arsenic in deer is similar to that found in other foods (eg. 10 - 75% is inorganic arsenic), arsenic exposure levels are well below levels known to cause adverse health effects in humans. Arsenic would not occur purely in the inorganic form in deer, because deer would be expected to metabolize arsenic as do all mammals. However, even if the very conservative assumption is used that all arsenic in deer is inorganic (the most toxic form), the risk estimates are no greater than that associated with consuming deer from off-post.

C. Due to the inherent uncertainties associated with arsenic, levels were also compared to establish standards or ARARs. Arsenic levels in deer were compared to FDA arsenic standards

for tolerable residues associated with feed additives and arsenical pesticide exposures in beef and pork (0.5 mg/kg and 0.7 mg/kg respectively). Again, most of these values have been established for the inorganic form of arsenic. The 95% upper confidence limits in deer from several sites on APG and off-post were similar and slightly higher than these values. Also, arsenic upper confidence limits in deer were compared to acceptable daily intake values for arsenic established by the World Health Organization but none of the arsenic intake values exceeded any of these ARARs.

D. Currently, there are no standard EPA methods available to evaluate lead in edible tissue. Therefore the FDA method for evaluating lead in shellfish was applied in this study. Maximum lead levels of concern were based on exposure factors (EPA standards and consumption data collected during the study) and on provisional tolerable total intake levels for the general and sensitive populations (children under 6 years of age, school age children, pregnant women, and adults). Lead levels in deer tissue were compared to these acceptable maximum levels. Overall, the lead levels in deer from both APG and offpost sites were within the acceptable limits.

E. Based on these data and the subsequent risk analysis, the health risk associated with consuming deer meat from APG is no greater than that associated with consuming deer meat from off-post. Therefore following the current hunting practices, consumption of APG deer should not present an elevated human health hazard.

VIII. PERSONNEL INVOLVED.

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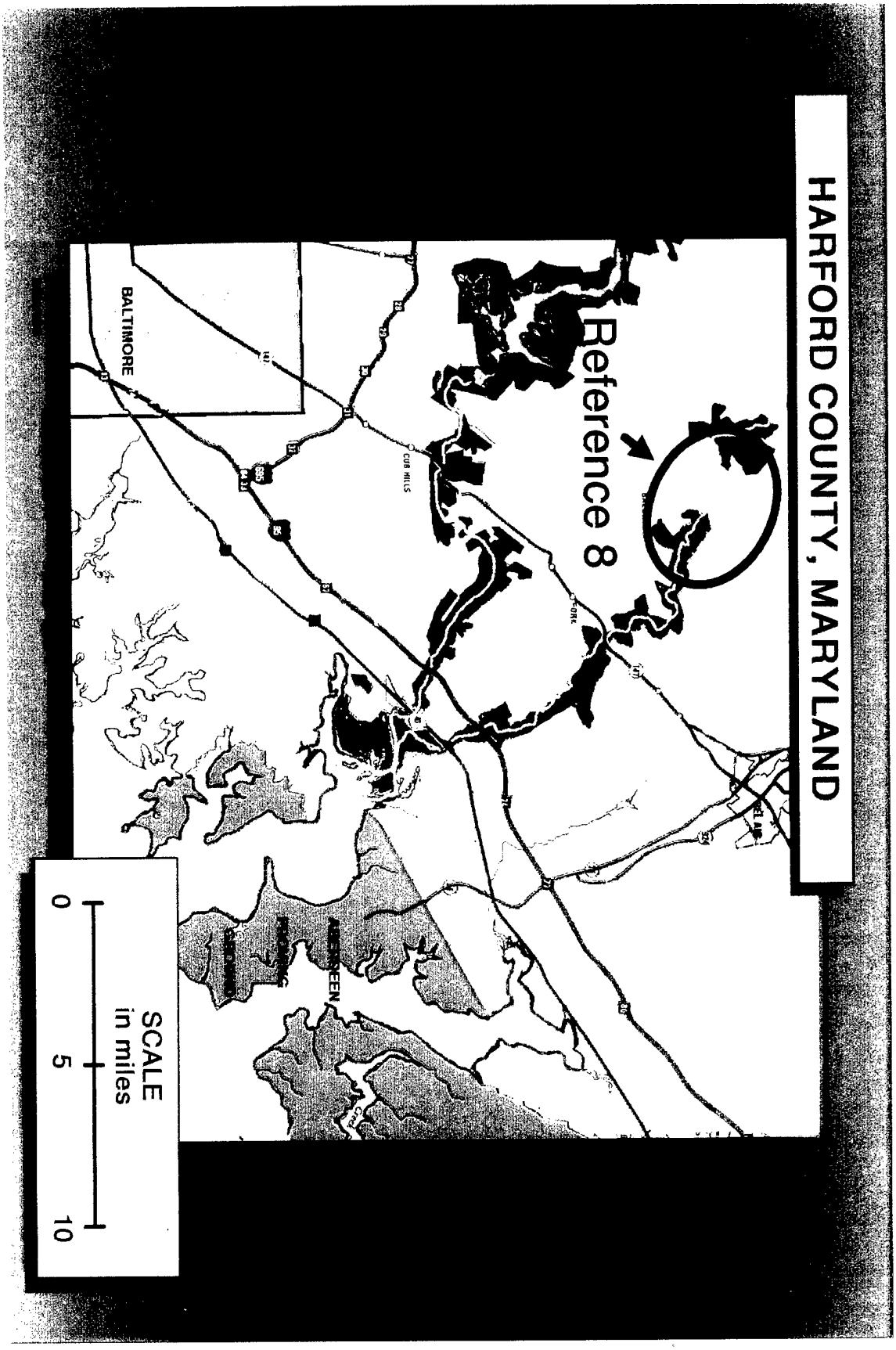
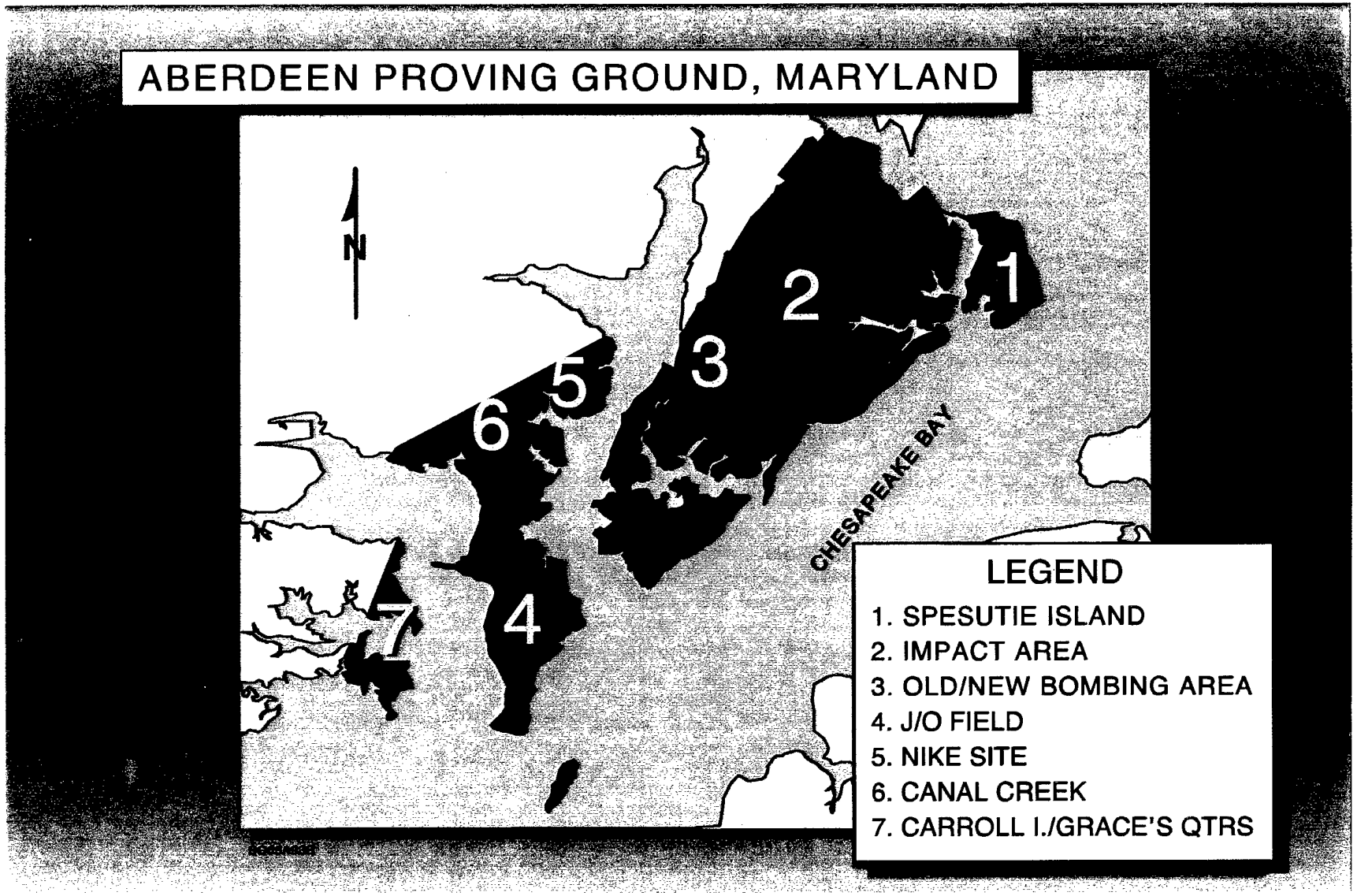
MAP 1 - APG and Reference Site





MAP 2 - Sample Locations on APG

TABLE 1

APG HUNTER'S QUESTIONNAIRE *(Total Responses = 103)*

1. Number of years you have hunted at APG? ***2.1 (median average)***

2. Number of deer you usually harvest from APG per year? ***2 (median average)***

3. Number of people in your household who consume your deer from APG including yourself? ***4 (median average)***

4. Do you save and consume the deer liver? ***20/103 = 19% Yes***

5. What percent of your venison/venison liver is consumed by you and your immediate family?

   93 % venison

   80 % venison liver

6. Disposition of remainder of venison/venison liver.

   a. give to friends ***61/103*** venison

      13/103 venison liver

   b. feed to pets ***17/103*** venison

      5/103 venison liver

   c. other (specify) ***2/10 (donate to college)***

7. Do you save and consume any other organs such as the kidney or the heart? If so, please specify what organ and how much. ***15/103 = 15% Yes (15/103 - heart, 2/103 kidney, 1/103 bone)***

TABLE 2: TOXICITY VALUES AND PROJECT REPORTING LEVELS

Chemical	PRL(mg/kg)	Method	RfD(mg/kg-d)	WOE	SF(mg/kg-d)
Explosives:					
RDX	0.10	USAEHA SOP 51.4	3.0E-3	C	1.1E-1
HMX	0.10		5.0E-2	D	---
1,3-DNB	0.05		1.0E-4	D	---
1,3,5-TNB	0.20		5.0E-5	NA	NA
2,4,6-TNT	0.10		5.0E-4	C	3.0E-2
2-A-4,6-DNT	0.10		5.0E-4	C	3.0E-2
4-A-2,6-DNT	0.20		5.0E-4	C	3.0E-2
2,6-DNT	0.05		NA	B2	6.8E-1
2,4-DNT	0.05		NA	B2	6.8E-1
Metals:					
As	0.025	USAEHA SOP 23	3.0E-4	A	1.7E+0*
Cd	0.025		1.0E-3	B1	++
Cr	0.025		5.0E-3	A	++
Hg	0.100	USAEHA SOP 10	3.0E-4	D	---
Pb	0.025		NA	B2	NA
Organochlorine pesticides:					
o,p'-DDD	0.01	USAEHA SOP 37.1	5.0E-4	B2	3.4E-1
p,p'-DDD	0.01		5.0E-4	B2	3.4E-1
o,p'-DDE	0.01		5.0E-4	B2	3.4E-1
p,p'-DDE	0.01		5.0E-4	B2	3.4E-1
o,p'-DDT	0.015		5.0E-4	B2	3.4E-1
p,p'-DDT	0.015		5.0E-4	B2	3.4E-1
Aroclors:					
1242	0.10	USAEHA SOP 37.1	NA	B2	7.7E-0
1016	0.10		NA	B2	7.7E-0
1248	0.10		NA	B2	7.7E-0
1254	0.10		NA	B2	7.7E-0
1260	0.10		NA	B2	7.7E-0

NA - not avaliable; compound under review by EPA
PRL - project reporting level
RfD - reference dose
WOE - weight of evidence
SF - slope factor
* the oral slope factor derived from the USEPA
unit risk concentration for drinking water (5.0E-5 ug/L)
++ slope factor for inhalation route only

TABLE 3: SITE IDENTIFICATION AND SAMPLING DATA

SITE	Field #	SEX	AGE(yrs)	WT(lbs)
1. Spesutie Island				
(AA)	1	male	4	145
n = 20	2	male	2	140
	3	male	3	119
	4	male	1	77
	5	male	1	91
	6	male	0	50
	7	male	0	55
	8	male	0	57
	9	male	0	52
	10	male	1	103
	11	female	1	75
	12	female	2	72
	13	female	2	67
	14	female	0	44
	15	female	6	86
	16	female	1	87
	17	female	0	36
	18	female	0	49
	19	female	1	80
	20	female	1	32
2. Impact Area				
(AA)	21	male	4	100
n = 20	22	male	3	108
	23	male	2	113
	24	male	3	121
	25	male	2	90
	26	male	1	87
	27	male	1	114
	28	male	2	100
	29	male	2	99
	30	male	2	111
	31	female	0	46
	32	female	5	86
	33	female	2	63
	34	female	2	85
	35	female	1	60
	36	female	2	87
	37	female	0	30
	38	female	1	95
	39	female	3	90
	40	female	2	74
3. Bombing Area				
(AA)	41	male	0	41
n = 20	42	male	4	108
	43	male	3	93
	44	male	2	75
	45	male	3	104
	46	male	1	97
	47	male	1	73

TABLE 3: SITE IDENTIFICATION AND SAMPLING DATA

	48	male	2	91
	49	male	1	75
	50	male	N/A	115
	51	female	3	30
	52	female	0	42
	53	female	1	67
	54	female	0	47
	55	female	14	74
	56	female	0	24
	57	female	2	58
	58	female	0	48
	59	female	1	80
	60	female	9	66
4. J/O-Field (EA) n = 20	61	male	N/A	103
	62	male	N/A	100
	63	male	N/A	82
	64	male	N/A	128
	65	male	N/A	84
	66	male	N/A	90
	67	male	N/A	125
	68	male	N/A	126
	69	male	N/A	103
	70	male	N/A	110
	71	female	N/A	78
	72	female	N/A	83
	73	female	N/A	90
	74	female	N/A	45
	75	female	N/A	75
	76	female	N/A	71
	77	female	N/A	75
	78	female	N/A	78
	79	female	N/A	71
	80	female	N/A	45
5. Nike/Lauderick (EA) n = 21	81	male	N/A	125
	82	male	N/A	104
	83	male	N/A	102
	84	male	N/A	138
	85	male	N/A	47
	86	male	N/A	85
	87	male	N/A	105
	88	male	N/A	76
	89	male	N/A	91
	90	female	N/A	51
	91	female	N/A	103
	92	female	N/A	57
	93	female	N/A	86
	94	female	N/A	45
	95	female	N/A	72
	96	female	N/A	49

TABLE 3: SITE IDENTIFICATION AND SAMPLING DATA

	97	female	N/A	91
	98	female	N/A	44
	99	female	N/A	65
	115	female	N/A	105
	129	male	N/A	87
6. Westwood/Canal				
Creek	100	male	N/A	78
(EA)	101	male	N/A	110
n = 15	102	male	N/A	80
	103	male	N/A	100
	104	male	N/A	145
	105	male	N/A	100
	106	female	N/A	58
	107	female	N/A	60
	108	female	N/A	83
	109	female	N/A	92
	110	female	N/A	42
	111	female	N/A	N/A
	112	female	N/A	98
	113	male	N/A	100
	114	male	N/A	77
7. Graces Quarters				
Carroll Island	116	female	N/A	80
(EA)	117	female	N/A	N/A
n = 13	118	female	N/A	N/A
	119	female	N/A	N/A
	120	female	N/A	N/A
	121	female	N/A	N/A
	122	female	N/A	N/A
	123	female	N/A	N/A
	124	female	N/A	N/A
	125	male	N/A	N/A
	126	male	N/A	N/A
	127	male	N/A	N/A
	128	male	N/A	50
8. Gunpowder State				
Park	130	male	N/A	87
n = 20	131	male	N/A	82
	132	male	N/A	59
	133	male	N/A	52
	134	male	N/A	58
	135	male	N/A	100
	136	male	N/A	42
	137	male	N/A	52
	138	male	N/A	56
	139	male	N/A	63
	140	female	N/A	89
	141	female	N/A	85
	142	female	N/A	61
	143	female	N/A	108
	144	female	N/A	101

TABLE 3: SITE IDENTIFICATION AND SAMPLING DATA

145	female	N/A	102
146	female	N/A	90
147	female	N/A	59
148	female	N/A	42
149	female	N/A	65

age 0 = under 1 year

TABLE 4: EXPLOSIVES, PESTICIDES, AND PCBs DATA

Muscle and Liver

SITE	1	2	3	4	5	6	7	8
TNT	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
TNB	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
2,4-DNT	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
2,6-DNT	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
DNB	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
HMX	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
RDX	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
DDD	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
DDE	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
DDT	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl
PCBs	bprl	bprl	bprl	bprl	bprl	bprl	bprl	bprl

bprl = below project reporting levels

TABLE 5a: METALS DATA - MUSCLE

MEANS AND STANDARD DEVIATIONS - METALS DATA (mg/kg)

Parameter	Site	n	As	Cd	Cr	Hg	Pb
Mean	1	20	0.642	0.0166	0.943	0.050	0.532
Std Dev			0.160	0.0182	0.321	0.000	1.156
Range			0.366-0.845	0.0125-0.094	0.540-1.86	0.05-0.05	0.065-4.59
Mean	2	20	0.808	0.0144	0.966	0.0525	0.232
Std Dev			0.114	0.0058	0.204	0.0112	0.312
Range			0.570-0.98	0.125-0.032	0.190-1.26	0.05-0.1	0.063-1.46
Mean	3	20	0.683	0.0125	0.937	0.050	0.119
Std Dev			0.183	0.000	0.205	0.000	0.0600
Range			0.075-0.875	0.0125	0.740-1.73	0.05-0.05	0.045-0.243
Mean	4	20	0.672	0.0147	0.830	0.050	0.143
Std Dev			0.116	0.0096	0.246	0.000	0.106
Range			0.547-0.849	0.0125-0.0556	0.525-1.56	0.05-0.05	0.064-0.435
Mean	5	21	0.746	0.0310	0.893	0.050	0.377
Std Dev			0.176	0.0778	0.262	0.000	0.659
Range			0.085-0.911	0.125-0.369	0.500-1.71	0.05-0.05	0.061-2.59
Mean	6	15	0.352*	0.0139	0.931	0.050	0.270
Std Dev			0.220	0.0054	0.376	0.000	0.393
Range			0.137-0.812	0.0125-0.0125	0.625-2.15	0.05-0.05	0.035-1.64
Mean	7	13	0.683	0.0136	0.859	0.050	0.388
Std Dev			0.116	0.0039	0.140	0.000	0.381
Range			0.474-0.895	0.0125-0.0125	0.625-1.22	0.05-0.05	0.138-1.53
Mean	8	20	0.357*	0.0139	0.941	0.050	0.304
Std Dev			0.176	0.0052	0.295	0.000	0.318
Range			0.125-0.815	0.0125-0.0355	0.685-1.68	0.05-0.05	0.134-1.6

* indicates significantly lower mean values

TABLE 5b: METALS DATA - LIVER

MEANS AND STANDARD DEVIATIONS - METALS (mg/kg)

Parameter	Site	n	As	Cd	Cr	Hg	Pb
Mean	1	20	0.723	0.0674*	1.816	0.0525	0.542
Std Dev			0.137	0.0742	3.041	0.0112	1.34
Range			0.323-0.961	0.0125-0.262	0.391-1.64	0.050-0.10	0.073-1.49
Mean	2	20	0.812	0.228	0.873	0.050	0.11
Std Dev			0.161	0.237	0.147	0.0	0.097
Range			0.268-1.01	0.0125-0.735	0.645-1.08	0.050	0.021-0.339
Mean	3	20	0.709	0.198	0.806	0.050	0.158
Std Dev			0.141	0.192	0.21	0.0	0.211
Range			0.370-1.01	0.0125-0.743	0.675-1.67	0.050	0.065-1.01
Mean	4	20	0.581	0.112	0.740	0.122	0.110
Std Dev			0.148	0.112	0.232	0.284	0.0547
Range			0.059-0.701	0.0125-0.451	0.107-1.17	0.050-1.32	0.062-0.240
Mean	5	21	0.709	0.0989*	0.825	0.073	0.112
Std Dev			0.127	0.0903	0.129	0.106	0.108
Range			0.329-1.05	0.0125-0.290	0.405-1.01	0.050-0.53	0.0125-0.390
Mean	6	15	0.452*	0.0945*	0.827	0.050	0.244
Std Dev			0.315	0.0969	0.120	0.0	0.435
Range			0.156-0.961	0.0125-0.365	0.649-1.01	0.05	0.0125-1.75
Mean	7	13	0.903	0.179	0.909	0.050	0.148
Std Dev			0.103	0.110	0.094	0.0	0.030
Range			0.827-1.14	0.055-0.413	0.728-1.10	0.050	0.094-0.202
Mean	8	20	0.477*	0.0723*	1.14	0.050	0.191
Std Dev			0.257	0.0567	0.979	0.0	0.107
Range			0.131-0.909	0.027-0.301	0.710-5.26	0.050	0.104-0.290

* indicates significantly lower mean values

TABLE 5c: LEAD DATA – MUSCLE and LIVER

Site	Muscle Mean	(mg/kg) UCL	Liver Mean	(mg/kg) UCL
1	0.532	1.04	0.542	1.13
2	0.232	0.369	0.110	0.153
3	0.119	0.145	0.158	0.250
4	0.143	0.189	0.110	0.134
5	0.377	0.659	0.112	0.158
6	0.270	0.469	0.244	0.464
7	0.388	0.595	0.148	0.164
8	0.304	0.443	0.191	0.238
APG	0.460	0.867	0.0755	0.138
ES	0.316	0.424	0.0130	0.0130

APG – Pilot Study APG area
ES – Pilot Study Eastern Shore
UCL – 95% Upper Confidence Limit

TABLE 5d: PILOT STUDY MEANS AND STANDARD DEVIATIONS (mg/kg)

	TISSUE				
METAL	MUSCLE	LIVER	KIDNEY	BONE	
Arsenic	0.895 (0.126)	1.648 (0.119)	0.0669 (0.0797)	6.567 (0.459)	
Cadmium	0.365 (0.257)	0.642 (0.373)	7.576* (4.251)	0.279 (0.270)	
Chromium	0.786 (0.181)	1.454 (0.487)	0.447 (0.0401)	0.363 (0.0989)	APG n = 12
Mercury	0.0256 (0.0373)	0.0167 (0.0129)	0.289* (0.240)	0.0954 (0.207)	
Lead	0.460 (0.719)	0.0755 (0.111)	0.295 (0.132)	0.793 (0.494)	

	TISSUE				
METAL	MUSCLE	LIVER	KIDNEY	BONE	
Arsenic	0.824 (0.177)	1.573 (0.040)	0.332 (0.572)	7.640* (1.0249)	
Cadmium	0.852* (0.555)	0.337 (0.0365)	1.105 (0.944)	0.289 (0.252)	
Chromium	0.936 (0.179)	2.670 (2.458)	1.735* (2.024)	0.363 (0.244)	Eastern Shore n = 5
Mercury	0.0169 (0.0154)	0.0177 (0.0134)	0.0225 (0.0164)	0.0249 (0.0267)	
Lead	0.316 (0.123)	0.0130 (0.000)	0.425 (0.171)	0.370 (0.189)	

Standard Deviations given in parentheses

* Denotes significantly higher means

TABLE 6a: NONCANCER RISK CALCULATIONS - MUSCLE

Site	Chemical	UCL (mg/kg)	RfD (mg/kg-d)	Intake (mg/kg-d)	HQ
1	As	0.712	3.0E-4	2.57E-4	8.6E-1
	Cd	0.025	1.0E-3	8.89E-6	8.9E-3
	Cr	1.08	5.0E-3	3.92E-4	7.8E-2
	Hg	0.050	3.0E-4	1.81E-5	6.0E-2
				HI =	1.0E+0
2	As	0.858	3.0E-4	3.10E-4	1.0E+0
	Cd	0.017	1.0E-3	6.13E-6	6.1E-3
	Cr	1.05	5.0E-3	3.82E-4	7.6E-2
	Hg	0.0574	3.0E-4	2.08E-5	6.9E-2
				HI =	1.2E+0
3	As	0.763	3.0E-4	2.76E-4	9.2E-1
	Cd	0.0125	1.0E-3	4.52E-6	4.5E-3
	Cr	1.03	5.0E-3	3.71E-4	7.4E-2
	Hg	0.050	3.0E-4	1.81E-5	6.0E-2
				HI =	1.1E+0
4	As	0.723	3.0E-4	2.61E-4	8.7E-1
	Cd	0.019	1.0E-3	6.83E-6	6.8E-3
	Cr	0.938	5.0E-3	3.39E-4	6.8E-2
	Hg	0.050	3.0E-4	1.81E-5	6.0E-2
				HI =	1.0E+0
5	As	0.821	3.0E-4	2.97E-4	9.9E-1
	Cd	0.064	1.0E-3	2.32E-5	2.3E-2
	Cr	1.01	5.0E-3	3.63E-4	7.3E-2
	Hg	0.050	3.0E-4	1.81E-5	6.0E-2
				HI =	1.1E+0
6	As	0.463	3.0E-4	1.67E-4	5.6E-1
	Cd	0.017	1.0E-3	6.01E-6	6.0E-3
	Cr	1.12	5.0E-3	4.05E-4	8.1E-2
	Hg	0.050	3.0E-4	1.81E-5	6.0E-2
				HI =	7.1E-1
7	As	0.746	3.0E-4	2.70E-4	9.0E-1
	Cd	0.016	1.0E-3	5.69E-6	5.7E-3
	Cr	0.936	5.0E-3	3.38E-4	6.8E-2
	Hg	0.050	3.0E-4	1.81E-5	6.0E-2
				HI =	1.0E+0
8	As	0.434	3.0E-4	1.57E-4	5.2E-1
	Cd	0.016	1.0E-3	5.85E-6	5.9E-3
	Cr	1.07	5.0E-3	3.87E-4	7.7E-2
	Hg	0.050	3.0E-4	1.81E-5	6.0E-2
				HI =	6.6E-1

TABLE 6b: NONCANCER RISK CALCULATIONS – LIVER

Site	Chemical	UCL (mg/kg)	RfD (mg/kg-d)	Intake (mg/kg-d)	HQ
1	As	0.783	3.0E-4	3.43E-5	1.1E-1
	Cd	0.100	1.0E-3	4.38E-6	4.4E-3
	Cr	3.15	5.0E-3	1.38E-4	2.8E-2
	Hg	0.057	3.0E-4	2.52E-6	8.4E-3
				HI =	1.5E-1
2	As	0.882	3.0E-4	3.87E-5	1.3E-1
	Cd	0.332	1.0E-3	1.45E-5	1.4E-2
	Cr	0.937	5.0E-3	4.12E-5	8.2E-3
	Hg	0.050	3.0E-4	2.19E-6	7.3E-3
				HI =	1.6E-1
3	As	0.771	3.0E-4	3.38E-5	1.3E-1
	Cd	0.282	1.0E-3	1.24E-5	1.2E-2
	Cr	0.898	5.0E-3	3.94E-5	7.9E-3
	Hg	0.050	3.0E-4	2.19E-6	7.3E-3
				HI =	1.6E-1
4	As	0.646	3.0E-4	2.83E-5	9.4E-2
	Cd	0.161	1.0E-3	7.06E-6	7.1E-3
	Cr	0.842	5.0E-3	3.96E-5	7.4E-3
	Hg	0.246	3.0E-4	1.08E-5	3.6E-2
				HI =	1.4E-1
5	As	0.763	3.0E-4	3.35E-5	1.1E-1
	Cd	0.994	1.0E-3	6.03E-6	6.0E-3
	Cr	0.880	5.0E-3	3.86E-5	7.7E-3
	Hg	0.118	3.0E-4	5.19E-6	1.7E-3
				HI =	1.2E-1
6	As	0.144	3.0E-4	6.29E-6	2.1E-2
	Cd	0.143	1.0E-3	4.36E-5	4.4E-2
	Cr	0.888	5.0E-3	3.89E-5	7.8E-3
	Hg	0.050	3.0E-4	2.19E-6	7.3E-3
				HI =	8.0E-2
7	As	0.960	3.0E-4	4.20E-5	1.4E-1
	Cd	0.239	1.0E-3	1.05E-5	1.0E-2
	Cr	0.960	5.0E-3	4.21E-5	3.8E-3
	Hg	0.050	3.0E-4	2.19E-6	7.3E-3
				HI =	1.6E-1
8	As	0.590	3.0E-4	2.58E-5	8.6E-2
	Cd	0.097	1.0E-3	4.26E-6	4.2E-3
	Cr	1.57	5.0E-3	6.88E-5	1.4E-2
	Hg	0.050	3.0E-4	2.19E-6	7.3E-3
				HI =	1.1E-1

TABLE 6c: PILOT STUDY NONCANCER RISK CALCULATIONS

Site	Chemical	UCL (mg/kg)	RfD (mg/kg-d)	Intake (mg/kg-d)	HQ	
APG	As	0.966	3.0E-4	3.49E-4	1.2E+0	
	Cd	0.510	1.0E-3	1.84E-4	1.8E-1	
	Cr	0.888	5.0E-3	3.21E-4	6.4E-2	
	Hg	0.047	3.0E-4	1.70E-5	5.7E-2	
				HI =	1.5E+0	Muscle
Eastern	As	0.979	3.0E-4	3.54E-4	1.2E-0	
Shore	Cd	1.34	1.0E-3	4.85E-4	4.8E-1	
	Cr	1.09	5.0E-3	3.94E-4	7.9E-2	
	Hg	0.030	3.0E-3	1.08E-5	3.6E-2	
				HI =	1.8E+0	
APG	As	1.72	3.0E-4	7.54E-5	2.5E-1	
	Cd	0.853	1.0E-3	3.74E-5	3.7E-2	
	Cr	1.73	5.0E-3	7.58E-5	1.5E-2	
	Hg	0.024	3.0E-3	1.05E-6	3.5E-4	
				HI =	3.0E-1	Liver
Eastern	As	1.61	3.0E-4	7.06E-5	2.4E-1	
Shore	Cd	0.369	1.0E-3	1.62E-5	1.6E-2	
	Cr	4.82	5.0E-3	2.11E-4	4.2E-2	
	Hg	0.029	3.0E-3	1.27E-6	4.2E-4	
				HI =	3.0E-1	

TABLE 7a: CANCER RISK CALCULATIONS

Chemical	Site	UCL (mg/kg)	SF (per mg/kg-d)	Intake (mg/kg-d)	CR	
As	1	0.712	1.7E+0*	1.10E-4	2E-4	
	2	0.858	1.7E+0*	1.33E-4	2E-4	
	3	0.763	1.7E+0*	1.18E-4	2E-4	
	4	0.723	1.7E+0*	1.12E-4	2E-4	MUSCLE
	5	0.821	1.7E+0*	1.27E-4	2E-4	
	6	0.463	1.7E+0*	7.18E-5	1E-4	
	7	0.746	1.7E+0*	1.16E-4	2E-4	
	8	0.434	1.7E+0*	6.73E-5	1E-4	
As	1	0.783	1.7E+0*	1.84E-5	3E-5	
	2	0.876	1.7E+0*	2.06E-5	3E-5	
	3	0.771	1.7E+0*	1.81E-5	3E-5	
	4	0.646	1.7E+0*	1.52E-5	3E-5	LIVER
	5	0.763	1.7E+0*	1.80E-5	3E-5	
	6	0.611	1.7E+0*	1.43E-5	2E-5	
	7	0.960	1.7E+0*	2.25E-5	4E-5	
	8	0.590	1.7E+0*	1.39E-5	2E-5	

TABLE 7b: PILOT STUDY CANCER RISK CALCULATIONS

Chemical	Site	UCL (mg/kg)	SF (per mg/kg-d)	Intake (mg/kg-d)	CR	
As	APG	0.966	1.7E+0*	1.50E-4	3E-4	
	Eastern	0.979	1.7E+0*	1.52E-4	3E-4	MUSCLE
	Shore					
As	APG	1.72	1.7E+0*	3.23E-5	5E-5	
	Eastern	1.61	1.7E+0*	3.02E-5	5E-5	LIVER
	Shore					

*** The oral slope factor for arsenic was calculated from the EPA drinking water unit risk concentration**

TABLE 8: DERIVATIONS

MEAN AND STANDARD DEVIATION

$$\text{Mean} = \frac{\Sigma x}{n}$$

$$\text{Std Dev} = \sqrt{\frac{\Sigma x^2 - \frac{(\Sigma x)^2}{n}}{n - 1}}$$

95% UPPER CONFIDENCE LEVEL (UCL)

$\bar{x} + 1.96(\text{std dev}/\sqrt{n})$

NONCANCER RISK

HAZARD QUOTIENT (HQ) = INTAKE/RfD

Intake = CF x IR x FI x EF x ED/BW x AT
- Concnetration Factor (CF) = UCL
- Ingestion Rate (IR) = 0.28 kg meat/meal
- Fraction Ingested (FI) = 100%
- Exposure Frequency (EF) – muscle = 33 meals/year
  – liver = 4 meals/year
- Exposure Duration (ED) = 30 years
- Body Weight (BW) = 70 kg
- Average Time of Exposure (AT) = ED x 365(days/year)

RfD = Reference Dose (mg/kg–d)
Hazard Index (HI) = sum of HQs

CANCER RISK

CANCER RISK (CR) = INTAKE x SLOPE FACTOR

Intake = CF x IR x FI x EF x ED/BW x AT
- Concnetration Factor (CF) = UCL
- Ingestion Rate (IR) = 0.28 kg meat/meal
- Fraction Ingested (FI) = 100%
- Exposure Frequency (EF) – muscle = 33 meals/year
  – liver = 4 meals/year
- Exposure Duration (ED) = 30 years
- Body Weight (BW) = 70 kg
- Average Time of Exposure (AT) = 70 years x 365 (days/year)

APPENDIX A

Aberdeen Proving Ground

Site 1 - Spesutie Island. Spesutie Island is 2050 acre restricted area on APG bordered by the Chesapeake Bay and the Aberdeen area of APG. Areas of interest include an old dump site and a concrete lined burn trench. Chemicals reportedly discarded in the old dump area include: amines, urethanes, boron compounds, nitrogen fluorides, perchlorides, nitrosamines and other nitro compounds (see ref 1). The trench was used from 1917 through the late 1950's for tank testing and as a burning trench for various chemicals including chromium compounds, petroleum, oil, and lubricants, nitropolyhalogens, and hexanitrate diphenyls (see reference 1). Chemical characterization has not been completed for both areas.

Site 2 - Impact Area. The Impact Area has in the past and is currently being used for testing and evaluation of Army ordnance to include ballistics testing using a wide variety of ammunition and depleted uranium projectile testing. Currently, USAEHA is conducting an extensive soil, sediment, and water analysis of this area to characterize the type and extent of contamination. Also for the past several years, the Combat Systems and Test Activities has been conducting a depleted uranium body burden study of deer from this area (see reference 2).

Site 3 - Old/New Bombing Area. Old Bombing Field (OBF) and New Bombing Field (NBF) are active firing ranges. Burning and demolition of munitions have occurred in both areas. In 1981, Environmental Science and Engineering (see ref 1) reported that 99% of all disposal of munitions took place at the OBF, with some demolition and burning of propellants and incendiaries taking place at NBF. Currently, open burning and demolition operations only take place at the OBF. Previous sampling rounds at OBF and NBF did not find significant migration of contaminants (see reference 17). Surface soil at both areas is contaminated with trace amounts of explosives.

Edgewood Area

Site 4 - J/O-Field. J-Field is a hazardous waste and ordnance disposal site located on the southern end of Gunpowder Neck of Edgewood Area. Historically, J-Field was used for open burning/open detonation for the disposal of chemical agents, explosives, white phosphorus, and organic solvents. Portions of J-Field are still used for detonation or emergency disposal operations (see reference 3).

O-Field is a former test range and hazardous waste and ordnance disposal site located in the middle of the Gunpowder Neck in the Edgewood Area. The O-Field was used for the disposal of chemical warfare agents, munitions, contaminated equipment, and various other hazardous waste materials during the 1940's and early 1950's (see reference 3).

Site 5 - Lauderick Creek/Nike Site. The Lauderick Creek study area is located in the northeastern portion of the Edgewood Area, adjacent to the northern boundary of the installation.

The Nike site within this study area was used by the U.S. Army Chemical School for training in chemical warfare activities. The Nike Missile Battery was subsequently constructed on some of the school fields where missiles were stored and maintained until 1973 (see reference 3).

Site 6 - Westwood/Canal Creek Area. The Westwood study area is located near the northwestern installation boundary of the Edgewood Area of APG along the Gunpowder River. This area has been used for incendiary bomb testing, radiological defense training, pyrotechnic munitions testing, mustard contamination and decontamination testing, demilitarization testing, and training. Other uses include the storage of low level radioactive materials, landfilling, and storage of unknown chemical materials (see reference 3).

The Canal Creek study area is a watershed located in the northern section of the Edgewood Area. This area is a large industrial sector of APG that has supported the majority of APG's former chemical agent, smoke/incendiary, and protective-clothing manufacturing operations. Portions of the Canal Creek area also were used for landfilling sanitary wastes and for disposing for production waste. Other activities in the Canal Creek Area include operation of machine and maintenance shop garages, fabrication of metal parts, degreasing, and metal plating (see reference 3).

Site 7 - Graces Quarters/Carroll Island. Graces Quarters is located on the west side of the Gunpowder River. It is a peninsula bounded by the Gunpowder River to the east, Dundee Creek to the west, Saltpeter Creek to the south, and the Hammerman Area of Gunpowder State Park to the north. This area was used as an open-air testing area for munitions and chemical agents. The area also was used for the disposal (by open-burning and burial) of solid wastes for chemical agent test operations including decontamination studies involving distilled mustard (HD), the nerve agent VX, and fuming nitric acid (see reference 3).

Carroll Island is located between the Saltpeter and Seneca Creeks, which connect on the west side of the island to separate it from the mainland. This area was used for open-air testing of nerve agents, incapacitating agents, and smoke and incendiary munitions. Solid wastes generated during testing were disposed of by burial and by open burning onsite (see reference 3).

Reference Areas

Site 8 - Gunpowder State Park (Sweet Air Parcel). The Sweet Air Parcel of Gunpowder Falls State Park is located 25 miles north west of APG (see map 1). This area is physically separated from APG by a major interstate (I-95), and it is presumed that APG deer have no access to this area. Public hunting is by special permit only, and is strictly managed by the Maryland Department of Natural Resources.

Eastern Shore - Stillwater Creek Area The Stillwater Creek area is located across the Chesapeake Bay from APG on the Eastern Shore of Maryland. This is a private hunting area.

REFERENCES

1. Environmental Science and Engineering, Inc. 1981. Installation Assessment of Aberdeen Proving Ground, Aberdeen Area. Prepared for U.S. Army Toxic and Hazardous Materials Agency, Environmental Safety Division, Aberdeen Proving Ground, Maryland. Report No. 301.

2. Environmental Science and Engineering, Inc. 1982. Results of a Limited Sampling and Analysis Program for Burning Ground/Demolition Areas Located on the Aberdeen Area of Aberdeen Proving Ground. Prepared for U.S. Army Toxic and Hazardous Materials Agency, Field Systems Division, Aberdeen Proving Ground, Maryland. Report No. 301s.

3. U.S. Army Environmental Center, March 1993, ICF Kaiser Engineers, Inc. Technical Plan for the Risk and Biological Impact Assessment at U.S. Army Aberdeen Proving Ground, Maryland. Prepared for Directorate of Safety Health and Environment, Aberdeen Proving Ground, Maryland.

MARYLAND DEPARTMENT OF NATURAL RESOURCES

WILDLIFE DIVISION

APPLICATION FOR WILDLIFE PERMIT/LICENSE RENEWAL

INSTRUCTIONS

A. THIS IS AN APPLICATION FOR THE REISSUANCE OF A WILDLIFE PERMIT/LICENSE. REVIEW ALL THE INFORMATION IN PARTS 1-9 AND 13-14, MAKING ANY NEEDED CORRECTIONS IN THE SPACE TO THE RIGHT.

B. COMPLETE PARTS 17 (IF NECESSARY), 18 AND 19, THEN RETURN WITH FEE SHOWN IN PART 16 TO PERMITS COORDINATOR, WILDLIFE DIVISION, 580 TAYLOR AVE., ANNAPOLIS, MD 21401. MAKE CHECKS PAYABLE TO THE "DEPARTMENT OF NATURAL RESOURCES."

C. CONDITIONS AND AUTHORIZATIONS AS DETAILED ON YOUR CURRENT PERMIT WILL REMAIN IN FORCE; DESCRIBE ANY REQUESTED CHANGES IN CONDITIONS OF PERMIT ON AN ATTACHED SHEET OF PAPER.

CURRENT INFORMATION	CORRECTED/NEW INFORMATION
US Army Env. Hygiene Agency ATTN: HSHB-MO-T Bldg. E2100 Aberdeen Proving Ground MD 21010-	1. NAME 2. STREET 3. CITY 4. STATE / ZIP 5. COUNTY Harford
6. PHONE-HOME	
7. PHONE-WORK 410-671-3980	
8. NAME AND TITLE OF PRINCIPAL OFFICER (if #1 is a business) Janet E. Whaley, DVM	
	WRITE SOCIAL SECURITY # (OR FED. TAX #) BELOW IF NOT LISTED IN BOX #9
9. SOCIAL SECURITY OR FEDERAL TAX # ABERDEENJW	
10. TYPE Scientific Collecting	NOTE: A NEW PERMIT # WILL BE ISSUED ANNUALLY
11. CURRENT PERMIT NUMBER SCO-16636	12. NEW PERMIT NUMBER
13. FEDERAL PERMIT # (if applicable)	
14. LOCATION WHERE AUTHORIZED ACTIVITY MAY BE CONDUCTED (if applicable) Gunpowder Falls State Park - Sweet Air Parcel	

15. NEW PERMIT/LICENSE WILL BE EFFECTIVE: 01-01-95 AND EXPIRE: 12-31-95

16. FEE $ 10.00

17. COMPLIANCE WITH THE SPECIAL CONDITIONS LISTED BELOW ARE NECESSARY FOR PERMIT RENEWAL:

An annual report summarizing permit activity must accompany renewal.

18. CHECK ONE OF THE FOLLOWING TO COMPLY WITH MARYLAND'S WORKMEN COMPENSATION ACT (ARTICLE 1-401).

I AM :

___ SUPPLYING DNR WITH A CERTIFICATE OF INSURANCE.

___ SUPPLYING DNR WITH INSURANCE BINDER NUMBER _____.

___ SELF-EMPLOYED OR EMPLOY ONLY FAMILY MEMBERS, AND THEREFORE I AM NOT REQUIRED TO COMPLY WITH THIS LAW.

FOR DEPARTMENT USE ONLY

OTHER 919 X 16636

19. I HEREBY APPLY FOR RENEWAL OF THE ABOVE PERMIT/LICENSE AND CERTIFY UNDER PENALTY OF PERJURY THAT THE INFORMATION HEREIN IS TRUE AND CORRECT TO THE BEST OF MY KNOWLEDGE, INFORMATION AND BELIEF.

SIGNATURE OF APPLICANT DATE

QUESTIONS? CONTACT PERMITS COORDINATOR, FOREST, PARK AND WILDLIFE SERVICE, TAWES STATE OFFICE BLDG., ANNAPOLIS, MD 21401; (410) 974-3195. DNR-FPWS-0465 (04/90)

APPENDIX A

SAMPLING SITE DESCRIPTIONS

APPENDIX A

Aberdeen Proving Ground

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Carroll Island is located between the Saltpeter and Seneca Creeks, which connect on the west side of the island to separate it from the mainland. This area was used for open-air testing of nerve agents, incapacitating agents, and smoke and incendiary munitions. Solid wastes generated during testing were disposed of by burial and by open burning onsite (see reference 3).

Reference Area

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2. Environmental Science and Engineering, Inc. 1982. Results of a Limited Sampling and Analysis Program for Burning Ground/Demolition Areas Located on the Aberdeen Area of Aberdeen Proving Ground. Prepared for U.S. Army Toxic and Hazardous Materials Agency, Field Systems Division, Aberdeen Proving Ground, Maryland. Report No. 301s.

3. U.S. Army Environmental Center, March 1993, ICF Kaiser Engineers, Inc. Technical Plan for the Risk and Biological Impact Assessment at U.S. Army Aberdeen Proving Ground, Maryland. Prepared for Directorate of Safety Health and Environment, Aberdeen Proving Ground, Maryland.

MARYLAND DEPARTMENT OF NATURAL RESOURCES

WILDLIFE DIVISION

WILDLIFE PERMIT/LICENSE

1. PERMITTEE

US Army Env. Hygiene Agency
ATTN: HSHB-MO-T
Bldg. E2100
Aberdeen Proving Ground MD 21010-

2. PHONE-HOME

WORK
410-671-3980

3. PERMITTEE ID (SSN, FT#, ETC.)
ABERDEENJW

4. AUTHORITY-STATUTE(S)

ACM 10-909

REGULATION(S)
COMAR 08.03.09.06

5. NUMBER
SCO-16636

6. FEDERAL PERMIT # (if applicable)

7. EFFECTIVE
01-05-94

8. EXPIRES
12-31-94

9. TYPE
Scientific Collecting

10. NAME AND TITLE OF PRINCIPAL OFFICER (if #1 is a business)
Janet E. Whaley, DVM

11. LOCATION WHERE AUTHORIZED ACTIVITY MAY BE CONDUCTED (if applicable)
Gunpowder Falls State Park -
Sweet Air Parcel

12. CONDITIONS AND AUTHORIZATIONS:

A. CONDITIONS IN STATE LAW AND REGULATIONS CITED IN BLOCK #4 ABOVE, ARE HEREBY MADE A PART OF THIS PERMIT/LICENSE. ALL ACTIVITIES AUTHORIZED HEREIN MUST BE CARRIED OUT IN ACCORD WITH AND FOR THE PURPOSES DESCRIBED IN THE APPLICATION SUBMITTED. CONTINUED VALIDITY, OR RENEWAL, OF THIS PERMIT IS SUBJECT TO COMPLETE AND TIMELY COMPLIANCE WITH ALL APPLICABLE CONDITIONS, INCLUDING THE FILING OF ALL REQUIRED INFORMATION AND REPORTS.

B. THE VALIDITY OF THIS PERMIT IS ALSO CONDITIONED UPON STRICT OBSERVANCE OF ALL APPLICABLE FOREIGN, FEDERAL, LOCAL OR OTHER STATE LAWS.

C. Permittee, and designated subpermittees, are authorized to collect muscle and liver samples from hunter-killed white-tailed deer during the 1994 Sweet Air managed deer hunt. The samples shall be taken from 10 bucks and 10 does.

D. This permit does not authorize the taking of deer by the permittee.

E. Preliminary results of the study shall be provided to the Wildlife Division by January 31, 1995 and final results shall be provided upon completion of the study.

☐ ADDITIONAL CONDITIONS AND AUTHORIZATIONS ATTACHED ALSO APPLY

13. REPORTING REQUIREMENTS

Summary report of permit activity due by January 31, 1995.

ISSUED BY Mary S. Scanlan | TITLE PERMITS COORDINATOR | ISSUED 01-05-94

QUESTIONS? CONTACT PERMITS COORDINATOR, FOREST, PARK AND WILDLIFE SERVICE, TAWES STATE OFFICE BLDG., ANNAPOLIS, MD 21401; (410) 974-3195. DNR-FPWS-0456 (04/90)

APPENDIX B

METAL RESULTS

APPENDIX B

APG DEER METALS DATA – MUSCLE (ug/g)

Field #	SITE	SEX	As	Cd	Cr	Hg	Pb	AGE(yrs)	WT(lbs)
1	1	M	0.575	0.0125	0.745	0.05	0.155	4	145
2	1	M	0.540	0.0125	1.20	0.05	0.120	2	140
3	1	M	0.750	0.0125	0.830	0.05	0.067	3	119
4	1	M	0.392	0.0125	1.64	0.05	0.104	1	77
5	1	M	0.390	0.0125	0.540	0.05	0.088	1	91
6	1	M	0.600	0.094	1.05	0.05	4.59	0	50
7	1	M	0.366	0.0125	0.745	0.05	0.117	0	55
8	1	M	0.700	0.0125	0.760	0.05	0.101	0	57
9	1	M	0.495	0.0125	0.710	0.05	0.066	0	52
10	1	M	0.625	0.0125	0.670	0.05	0.366	1	103
11	1	F	0.424	0.0125	0.695	0.05	0.084	1	75
12	1	F	0.740	0.0125	1.06	0.05	0.159	2	72
13	1	F	0.735	0.0125	0.840	0.05	0.065	2	67
14	1	F	0.745	0.0125	0.815	0.05	0.088	0	44
15	1	F	0.765	0.0125	0.890	0.05	0.068	6	86
16	1	F	0.760	0.0125	0.900	0.05	2.93	1	87
17	1	F	0.840	0.0125	1.86	0.05	0.114	0	36
18	1	F	0.845	0.0125	1.06	0.05	0.107	0	49
19	1	F	0.830	0.0125	0.830	0.05	1.01	1	80
20	1	F	0.730	0.0125	1.02	0.05	0.234	1	32
21	2	M	0.715	0.0125	0.955	0.05	0.107	4	100
22	2	M	0.685	0.0125	1.00	0.05	0.105	3	108
23	2	M	0.865	0.0305	1.04	0.05	0.244	2	113
24	2	M	0.980	0.0125	1.26	0.05	0.137	3	121
25	2	M	0.650	0.0125	0.895	0.100	0.086	2	90
26	2	M	0.840	0.0125	0.990	0.05	0.098	1	87
27	2	M	0.570	0.0125	0.990	0.05	0.169	1	114
28	2	M	0.690	0.0125	1.03	0.05	0.120	2	100
29	2	M	0.860	0.0125	0.940	0.05	0.0855	2	99
30	2	M	0.975	0.0125	1.02	0.05	0.408	2	111
31	2	F	0.970	0.0125	1.16	0.05	0.099	0	46
32	2	F	0.850	0.0125	0.990	0.05	0.063	5	86
33	2	F	0.665	0.0125	1.06	0.05	0.126	2	63
34	2	F	0.755	0.0125	0.810	0.05	0.518	2	85
35	2	F	0.860	0.0125	0.965	0.05	0.316	1	60
36	2	F	0.840	0.0320	0.960	0.05	0.118	2	87
37	2	F	0.870	0.0125	0.190	0.05	0.095	0	30
38	2	F	0.880	0.0125	1.04	0.05	0.106	1	95
39	2	F	0.820	0.0125	1.01	0.05	0.176	3	90
40	2	F	0.815	0.0125	1.01	0.05	1.46	2	74

APG DEER METALS DATA – MUSCLE (ug/g)

41	3	M	0.755	0.0125	1.03	0.05	0.175	0	41
42	3	M	0.705	0.0125	1.02	0.05	0.243	4	108
43	3	M	0.700	0.0125	0.970	0.05	0.188	3	93
44	3	M	0.590	0.0125	0.940	0.05	0.196	2	75
45	3	M	0.570	0.0125	0.920	0.05	0.207	3	104
46	3	M	0.520	0.0125	0.975	0.05	0.159	1	97
47	3	M	0.560	0.0125	1.00	0.05	0.098	1	73
48	3	M	0.590	0.0125	1.00	0.05	0.126	2	91
49	3	M	0.565	0.0125	0.895	0.05	0.131	1	75
50	3	M	0.835	0.0125	1.73	0.05	0.140	NA	115
51	3	F	0.720	0.0125	0.840	0.05	0.045	3	30
52	3	F	0.810	0.0125	0.810	0.05	0.134	0	42
53	3	F	0.870	0.0125	0.870	0.05	0.078	1	67
54	3	F	0.875	0.0125	0.875	0.05	0.093	0	47
55	3	F	0.810	0.0125	0.810	0.05	0.051	14	74
56	3	F	0.740	0.0125	0.740	0.05	0.068	0	24
57	3	F	0.850	0.0125	0.850	0.05	0.046	2	58
58	3	F	0.790	0.0125	0.790	0.05	0.049	0	48
59	3	F	0.735	0.0125	0.840	0.05	0.076	1	80
60	3	F	0.075	0.0125	0.830	0.05	0.080	9	66
61	4	M	0.846	0.0125	0.735	0.05	0.088	NA	103
62	4	M	0.703	0.0125	0.525	0.05	0.149	NA	100
63	4	M	0.718	0.0125	0.670	0.05	0.074	NA	82
64	4	M	0.769	0.0125	0.715	0.05	0.0135	NA	128
65	4	M	0.781	0.0125	0.640	0.05	0.068	NA	84
66	4	M	0.752	0.0125	0.635	0.05	0.084	NA	90
67	4	M	0.814	0.0125	0.685	0.05	0.101	NA	125
68	4	M	0.776	0.0125	1.23	0.05	0.167	NA	126
69	4	M	0.784	0.0125	0.545	0.05	0.148	NA	103
70	4	M	0.849	0.0125	0.705	0.05	0.192	NA	110
71	4	F	0.556	0.0125	0.825	0.05	0.110	NA	78
72	4	F	0.563	0.0125	0.895	0.05	0.195	NA	83
73	4	F	0.553	0.0125	1.16	0.05	0.435	NA	90
74	4	F	0.550	0.0556	0.800	0.05	0.098	NA	45
75	4	F	0.577	0.0125	0.835	0.05	0.129	NA	75
76	4	F	0.590	0.0125	0.845	0.05	0.172	NA	71
77	4	F	0.593	0.0125	0.820	0.05	0.079	NA	75
78	4	F	0.558	0.0125	1.56	0.05	0.409	NA	78
79	4	F	0.551	0.0125	0.900	0.05	0.092	NA	71
80	4	F	0.547	0.0125	0.865	0.05	0.064	NA	45

APG DEER METALS DATA – MUSCLE (ug/g)

81	5	M	0.820	0.0125	1.41	0.05	2.59	NA	125
82	5	M	0.763	0.0125	0.810	0.05	0.065	NA	104
83	5	M	0.876	0.0437	1.03	0.05	0.341	NA	102
84	5	M	0.876	0.0125	0.770	0.05	0.090	NA	138
85	5	M	0.775	0.0125	0.970	0.05	0.192	NA	47
86	5	M	0.650	0.0125	0.855	0.05	0.341	NA	85
87	5	M	0.804	0.0125	0.845	0.05	0.066	NA	105
88	5	M	0.683	0.0125	0.590	0.05	0.094	NA	76
89	5	M	0.781	0.0125	0.785	0.05	0.139	NA	91
90	5	F	0.826	0.0125	0.985	0.05	0.071	NA	51
91	5	F	0.805	0.369	1.71	0.05	2.01	NA	103
92	5	F	0.859	0.0125	0.760	0.05	0.093	NA	57
93	5	F	0.911	0.0125	1.02	0.05	0.061	NA	86
94	5	F	0.0845	0.0125	0.500	0.05	0.134	NA	45
95	5	F	0.805	0.0125	0.750	0.05	0.184	NA	72
96	5	F	0.765	0.0125	0.935	0.05	0.542	NA	49
97	5	F	0.884	0.0125	0.880	0.05	0.090	NA	91
98	5	F	0.630	0.0125	0.800	0.05	0.165	NA	44
99	5	F	0.815	0.0125	0.700	0.05	0.092	NA	65
115	5	F	0.583	0.0125	0.760	0.05	0.130	NA	105
129	5	M	0.675	0.0125	0.880	0.05	0.436	NA	87
100	6	M	0.765	0.0125	1.08	0.05	0.054	NA	78
101	6	M	0.277	0.0125	0.760	0.05	0.049	NA	110
102	6	M	0.208	0.0125	0.830	0.05	0.363	NA	80
103	6	M	0.241	0.0333	2.15	0.05	1.64	NA	100
104	6	M	0.140	0.0125	0.820	0.05	0.154	NA	145
105	6	M	0.267	0.0125	0.675	0.05	0.115	NA	100
106	6	F	0.212	0.0125	0.790	0.05	0.137	NA	58
107	6	F	0.201	0.0125	0.767	0.05	0.194	NA	60
108	6	F	0.137	0.0125	1.24	0.05	0.035	NA	83
109	6	F	0.205	0.0125	0.625	0.05	0.125	NA	92
110	6	F	0.254	0.0125	0.675	0.05	0.098	NA	42
111	6	F	0.511	0.0125	0.880	0.05	0.298	NA	NA
112	6	F	0.812	0.0125	1.06	0.05	0.248	NA	98
113	6	M	0.484	0.0125	0.770	0.05	0.352	NA	100
114	6	M	0.559	0.0125	0.845	0.05	0.188	NA	77

APG DEER METALS DATA – MUSCLE (ug/g)

116	7	F	0.662	0.0125	0.855	0.05	0.402	NA	80
117	7	F	0.763	0.0125	0.830	0.05	0.280	NA	NA
118	7	F	0.495	0.0125	0.730	0.05	0.295	NA	NA
119	7	F	0.691	0.0125	0.980	0.05	0.160	NA	NA
120	7	F	0.895	0.0125	0.860	0.05	0.761	NA	NA
121	7	F	0.574	0.0125	0.625	0.05	0.194	NA	NA
122	7	F	0.711	0.0125	0.805	0.05	0.138	NA	NA
123	7	F	0.755	0.0267	0.810	0.05	0.297	NA	NA
124	7	F	0.755	0.0125	0.860	0.05	0.156	NA	NA
125	7	M	0.756	0.0125	0.895	0.05	0.235	NA	NA
126	7	M	0.474	0.0125	0.770	0.05	0.181	NA	NA
127	7	M	0.637	0.0125	1.22	0.05	0.419	NA	NA
128	7	M	0.714	0.0125	0.930	0.05	1.53	NA	50
130	8	M	0.596	0.0125	1.68	0.05	0.134	NA	87
131	8	M	0.144	0.0355	0.800	0.05	0.500	NA	82
132	8	M	0.213	0.0125	0.825	0.05	0.284	NA	59
133	8	M	0.303	0.0125	0.865	0.05	0.386	NA	52
134	8	M	0.321	0.0125	0.965	0.05	0.229	NA	58
135	8	M	0.390	0.0125	0.965	0.05	0.344	NA	100
136	8	M	0.272	0.0125	0.905	0.05	0.260	NA	42
137	8	M	0.289	0.0125	0.890	0.05	0.212	NA	52
138	8	M	0.363	0.0125	0.945	0.05	0.242	NA	56
139	8	M	0.250	0.0173	0.250	0.05	0.186	NA	63
140	8	F	0.235	0.0125	0.955	0.05	0.165	NA	89
141	8	F	0.382	0.0125	0.995	0.05	0.272	NA	85
142	8	F	0.266	0.0125	0.900	0.05	0.134	NA	61
143	8	F	0.393	0.0125	0.935	0.05	1.60	NA	108
144	8	F	0.382	0.0125	0.830	0.05	0.188	NA	101
145	8	F	0.325	0.0125	0.920	0.05	0.171	NA	102
146	8	F	0.125	0.0125	0.880	0.05	0.148	NA	90
147	8	F	0.735	0.0125	0.985	0.05	0.234	NA	59
148	8	F	0.815	0.0125	1.65	0.05	0.162	NA	42
149	8	F	0.345	0.0125	0.685	0.05	0.225	NA	65

* Indicates outliers
Shaded values = half of the detection limit

APG DEER METAL DATA – LIVER (mg/kg)

Field #	SITE	SEX	As	Cd	Cr	Hg	Pb	AGE(yrs)	WT(lbs)
1	1	M	0.641	0.0610	0.871	0.05	0.080	4	145
2	1	M	0.852	0.0125	0.841	0.05	0.078	2	140
3	1	M	0.323	0.0373	1.64	0.05	0.137	3	119
4	1	M	0.695	0.176	0.895	0.05	6.02*	1	77
5	1	M	0.719	0.0845	7.05*	0.05	0.073	1	91
6	1	M	0.590	0.0125	13.3*	0.05	1.49	0	50
7	1	M	0.792	0.0125	0.845	0.05	0.084	0	5
8	1	M	0.779	0.0427	0.929	0.05	0.136	0	57
9	1	M	0.961	0.0334	0.811	0.05	0.083	0	52
10	1	M	0.647	0.262	0.907	0.05	0.193	1	103
11	1	F	0.718	0.102	0.846	0.100	0.063	1	75
12	1	F	0.727	0.0765	0.793	0.05	0.117	2	72
13	1	F	0.720	0.0125	0.791	0.05	0.120	2	67
14	1	F	0.590	0.0125	0.391	0.05	0.296	0	44
15	1	F	0.630	0.232	0.792	0.05	0.220	6	86
16	1	F	0.762	0.0125	0.759	0.05	0.198	1	87
17	1	F	0.849	0.0327	0.946	0.05	0.087	0	36
18	1	F	0.790	0.0345	1.02	0.05	0.155	0	49
19	1	F	0.759	0.085	0.925	0.05	1.08	1	80
20	1	F	0.910	0.0125	0.967	0.05	0.104	1	32
21	2	M	0.919	0.302	0.938	0.05	0.102	4	100
22	2	M	0.869	0.735	1.04	0.05	0.339	3	108
23	2	M	1.01	0.0995	1.05	0.05	0.111	2	113
24	2	M	0.953	0.399	1.05	0.05	0.063	3	121
25	2	M	0.953	0.661	0.964	0.05	0.071	2	90
26	2	M	0.797	0.0254	0.850	0.05	0.159	1	87
27	2	M	0.887	0.296	0.976	0.05	0.129	1	114
28	2	M	0.834	0.235	1.05	0.05	0.206	2	100
29	2	M	0.954	0.467	1.08	0.05	0.048	2	99
30	2	M	0.862	0.0125	0.848	0.05	0.0295	2	111
31	2	F	0.695	0.0125	0.762	0.05	0.0452	0	46
32	2	F	0.739	0.080	0.819	0.05	0.127	5	86
33	2	F	0.268	0.0125	0.645	0.05	0.191	2	63
34	2	F	0.600	0.420	0.980	0.05	0.352	2	85
35	2	F	0.855	0.0125	0.658	0.05	0.065	1	60
36	2	F	0.759	0.525	0.810	0.05	0.027	2	87
37	2	F	0.779	0.0125	0.650	0.05	0.0210	0	30
38	2	F	0.871	0.0125	0.788	0.05	0.0350	1	95
39	2	F	0.818	0.210	0.814	0.05	0.055	3	90
40	2	F	0.808	0.0258	0.688	0.05	0.0320	2	74

shaded values represent residue levels below the DL

APG DEER METAL DATA – LIVER (mg/kg)

41	3	M	0.685	0.172	0.717	0.05	0.123	0	41
42	3	M	0.511	0.296	0.810	0.05	0.0795	4	108
43	3	M	0.370	0.606	0.745	0.05	0.0750	3	93
44	3	M	0.709	0.120	0.871	0.05	0.125	2	75
45	3	M	0.635	0.743	0.734	0.05	0.0740	3	104
46	3	M	0.654	0.0125	0.733	0.05	0.109	1	97
47	3	M	0.606	0.286	0.732	0.05	1.01	1	73
48	3	M	0.655	0.224	0.851	0.05	0.0650	2	91
49	3	M	0.868	0.223	1.67	0.05	0.126	1	75
50	3	M	0.616	0.0125	0.731	0.05	0.0740	NA	115
51	3	F	0.726	0.0990	0.709	0.05	0.0695	3	30
52	3	F	0.694	0.245	0.784	0.05	0.0870	0	42
53	3	F	0.757	0.292	0.834	0.05	0.346	1	67
54	3	F	0.745	0.0620	0.729	0.05	0.0945	0	47
55	3	F	0.922	0.0125	0.695	0.05	0.0705	14	74
56	3	F	0.867	0.0125	0.785	0.05	0.0740	0	24
57	3	F	0.687	0.151	0.714	0.05	0.160	2	58
58	3	F	0.699	0.0321	0.675	0.05	0.0885	0	48
59	3	F	0.758	0.128	0.784	0.05	0.0925	1	80
60	3	F	1.01	0.224	0.826	0.05	0.218	9	66
61	4	M	0.424	0.135	0.806	0.05	0.0755	NA	103
62	4	M	0.418	0.126	0.881	1.32	0.0675	NA	100
63	4	M	0.517	0.0125	0.782	0.05	0.0795	NA	82
64	4	M	0.625	0.0125	0.780	0.05	0.151	NA	128
65	4	M	0.582	0.293	0.816	0.05	0.102	NA	84
66	4	M	0.0585	0.0125	0.211	0.05	.0770	NA	90
67	4	M	0.528	0.451	0.783	0.05	0.0930	NA	125
68	4	M	0.579	0.193	0.866	0.05	0.0825	NA	126
69	4	M	0.596	0.0125	0.775	0.05	0.0695	NA	103
70	4	M	0.641	0.195	0.970	0.05	0.119	NA	110
71	4	F	0.674	0.0830	0.107	0.05	0.107	NA	78
72	4	F	0.641	0.108	0.730	0.05	0.112	NA	83
73	4	F	0.617	0.0125	0.605	0.05	0.0830	NA	90
74	4	F	0.663	0.0360	0.835	0.05	0.0620	NA	45
75	4	F	0.692	0.0950	0.738	0.05	0.240	NA	75
76	4	F	0.697	0.182	0.710	0.215	0.0756	NA	71
77	4	F	0.657	0.148	1.17	0.05	0.0810	NA	75
78	4	F	0.625	0.0810	0.675	0.05	0.262	NA	78
79	4	F	0.701	0.0125	0.873	0.05	0.108	NA	71
80	4	F	0.678	0.0417	0.689	0.05	0.158	NA	45

shaded values represent residue levels below the DL

APG DEER METAL DATA – LIVER (mg/kg)

81	5	M	0.708	0.0770	0.848	0.05	0.0480	NA	125
82	5	M	0.723	0.0125	0.968	0.05	0.390	NA	104
83	5	M	0.727	0.103	0.974	0.05	0.0990	NA	102
84	5	M	0.737	0.175	0.945	0.05	0.0735	NA	138
85	5	M	0.753	0.0255	0.860	0.05	0.139	NA	47
86	5	M	0.692	0.160	0.924	0.05	0.0620	NA	85
87	5	M	0.674	0.199	0.833	0.05	0.121	NA	105
88	5	M	0.329	0.0585	0.405	0.05	0.0515	NA	76
89	5	M	0.652	0.0125	0.763	0.05	0.101	NA	91
90	5	F	0.697	0.305	0.873	0.05	0.0610	NA	51
91	5	F	0.560	0.0125	0.758	0.05	0.0125	NA	103
92	5	F	0.693	0.0436	0.711	0.05	0.0850	NA	57
93	5	F	0.771	0.175	0.733	0.05	0.0125	NA	86
94	5	F	0.638	0.0530	0.853	0.05	0.0125	NA	45
95	5	F	0.749	0.0905	0.754	0.05	0.0125	NA	72
96	5	F	0.758	0.0125	0.755	0.05	0.0483	NA	49
97	5	F	0.681	0.119	0.847	0.05	0.354	NA	91
98	5	F	0.733	0.0125	0.778	0.535	0.265	NA	44
99	5	F	0.730	0.0125	0.909	0.05	0.0505	NA	65
115	5	F	1.05	0.128	1.01	0.05	0.153	NA	105
129	5	M	0.834	0.290	0.828	0.05	0.197	NA	87
100	6	M	0.727	0.191	0.850	0.05	0.0125	NA	78
101	6	M	0.195	0.147	0.750	0.05	0.149	NA	110
102	6	M	0.260	0.136	1.01	0.05	0.104	NA	80
103	6	M	0.262	0.138	0.734	0.05	0.0590	NA	100
104	6	M	0.738	0.116	0.668	0.05	1.75	NA	145
105	6	M	0.226	0.0125	0.649	0.05	0.108	NA	100
106	6	F	0.156	0.0125	0.759	0.05	0.103	NA	58
107	6	F	0.180	0.0263	0.830	0.05	0.127	NA	60
108	6	F	0.233	0.0125	1.00	0.05	0.0760	NA	83
109	6	F	0.161	0.125	0.706	0.05	0.0340	NA	92
110	6	F	0.210	0.0555	0.989	0.05	0.141	NA	42
111	6	F	0.717	0.0125	0.773	0.05	0.134	NA	NA
112	6	F	0.882	0.0555	0.927	0.05	0.158	NA	98
113	6	M	0.961	0.0125	0.895	0.05	0.558	NA	100
114	6	M	0.869	0.365	0.869	0.05	0.145	NA	77

shaded values represent residue levels below the DL

APG DEER METAL DATA – LIVER (mg/kg)

116	7	F	0.827	0.147	0.916	0.05	0.190	NA	80
117	7	F	0.830	0.185	0.938	0.05	0.126	NA	NA
118	7	F	0.848	0.0550	0.982	0.05	0.155	NA	NA
119	7	F	0.848	0.233	0.844	0.05	0.147	NA	NA
120	7	F	1.14	0.388	1.04	0.05	0.132	NA	NA
121	7	F	1.11	0.413	1.10	0.05	0.202	NA	NA
122	7	F	0.879	0.179	0.901	0.05	0.129	NA	NA
123	7	F	0.828	0.120	0.915	0.05	0.125	NA	NA
124	7	F	0.884	0.0910	0.855	0.05	0.129	NA	NA
125	7	M	0.848	0.138	0.728	0.05	0.168	NA	NA
126	7	M	0.888	0.122	0.845	0.05	0.151	NA	NA
127	7	M	0.938	0.186	0.877	0.05	0.173	NA	NA
128	7	M	0.878	0.0685	0.872	0.05	0.0940	NA	50
130	8	M	0.909	0.301	1.40	0.05	0.181	NA	87
131	8	M	0.337	0.0497	0.995	0.05	0.164	NA	82
132	8	M	0.145	0.0505	0.935	0.05	0.220	NA	59
133	8	M	0.849	0.0267	0.693	0.05	0.290	NA	52
134	8	M	0.387	0.0306	0.904	0.05	0.0890	NA	58
135	8	M	0.266	0.0550	5.26	0.05	0.177	NA	100
136	8	M	0.131	0.0715	0.871	0.05	0.231	NA	42
137	8	M	0.373	0.0463	0.987	0.05	0.193	NA	52
138	8	M	0.429	0.0615	0.962	0.05	0.127	NA	56
139	8	M	0.167	0.0780	0.959	0.05	0.139	NA	63
140	8	F	0.532	0.0740	0.816	0.05	0.148	NA	89
141	8	F	0.406	0.0645	0.980	0.05	0.209	NA	85
142	8	F	0.232	0.0520	0.921	0.05	0.189	NA	61
143	8	F	0.395	0.0830	0.904	0.05	0.155	NA	108
144	8	F	0.390	0.0422	1.03	0.05	0.0860	NA	101
145	8	F	0.393	0.0695	0.971	0.05	0.104	NA	102
146	8	F	0.855	0.0680	0.701	0.05	0.158	NA	90
147	8	F	0.705	0.0560	0.960	0.05	0.595	NA	59
148	8	F	0.770	0.0630	0.815	0.05	0.152	NA	42
149	8	F	0.865	0.102	0.840	0.05	0.219	NA	65

* Indicates outliers
Shaded values = half of the detection limit

APPENDIX B

STATISTICS

STATISTICAL EVALUATION

Statistical Evaluation. Metal data from the 1993/94 study were evaluated statistically to determine if inferences could be made between levels of metals and site, gender, and/or age. Data from the pilot study was not considered in this analysis because the study was conducted during the previous hunting season. All liver and muscle data were tested for normality using PROC UNIVARIATE in SAS. Logarithm and square root transformations of the data were also tested for normality. The data and the transformed data were not normally distributed. Therefore the data was analyzed using both parametric and nonparametric, rank transformation, approaches. The results were reported as means with standard deviations for ease of interpretation. A two-way analysis of variance (ANOVA) comparing site and gender was performed. Site and sex interactions were seen in several instances, but they were inconsistent. Since there were no consistent patterns between site and metals levels, the differences were considered biologically insignificant. Differences in metal concentrations among deer from all sample sites were compared using a one-way ANOVA and a Newman Keuls post-hoc test. In all cases, a $p < 0.05$ was considered significant. Several samples (muscle - # 91 arsenic and # 70 lead and liver - #34 for lead) were reanalyzed due to statistical nonconformity and these data are included in the statistical analysis.

It can be seen that there are slight differences in the results of the analyses of the parametric versus the nonparametric analyses. The analysis of the means, parametric approach, does not show statistically significant differences most likely due to the overall variability of the data. When the data is ranked, all the data is pooled and ranked from the lowest to the highest number. The statistical differences we observe here are due to one to two sites having the majority of the higher numbers and therefore the higher ranks. Whether these differences that we see are biologically significant is not addressed by these analyses.

Page 8, 3(a) Statistical evaluation:
After the second sentence add:

All liver and muscle data were tested for normality using PROC UNIVARIATE in SAS. Logarithm and square root transformations of the data were also tested for normality. The data and the transformed data were not normally distributed. Therefore the data was analyzed using both parametric and nonparametric, rank transformation, approaches. The results were reported as means with standard deviations for ease of interpretation. ...(start with "A two-way analysis...." delete what I've marked)

Interpretation of the analyses:

Liver:
including outliers (#4,5,6 and new data for 34)

	2-way ANOVA	2-way Ranks	1-way ANOVA	1-way rank
Cr	N.S.	SitexSex p<0.05	N.S.	Site p<0.05 8,7,1>3,4
Pb	N.S.	Site p<0.05 8>2,3,4,5 7>2,5	N.S.	Site p<0.05 8>2,3,4,5 7>2,5

same results

Liver: outliers excluded (#4,5,6)

	2-way ANOVA	2-way Ranks	1-way ANOVA	1-way rank
Cr	N.S.	SitexSex p<0.05	N.S.	Site p<0.05 8,7>3,4
Pb	N.S.	Site p<0.05 8>2,3,4,5 7>2,5	N.S.	Site p<0.05 8>2,3,4,5 7>2,5

Muscle:
no exclusions, all data with the new analyzed numbers

	2-way ANOVA	2-way Ranks	1-way ANOVA	1-way rank
As	SitexSex p<0.05	SitexSex p<0.05	Site p<0.05 2>1,6,8 5>6,8	Site p<0.05 2>1,3,4,6,7,8 5>6,8
Pb	N.S.	SitexSex p=0.0519 7>2,5	N.S.	Site p<0.05 8>1,3,4 7>1,2,3,4,5,6

There is no need to compare to the previous analysis since we were able to get all outliers replaced with reanalyzed numbers.

JOB FLAG

SATURN::LEE_RB
Entry 956
APGDER

Muscle Data
Arsenic + Pb
Reanalysis of data w/ reanalyzed data points

User Information:
- User Name: LEE_RB
- Account: DAKKRO
- UIC: LEE_RB
- Rights List: LEE_RB ([DAKKRO LEE_RB])

Submit:
- Queue: PR$1129A_QMS
- Priority: 100
- Time: 23-NOV-1994 10:59:37.61

Print:
- Queue: PR$1129A_QMS
- Device: QM1129::

Library: SYS$LIBRARY:QMS$DEVCTL20.TLB
Form: QMS$DEFAULT
Qualifiers: /QUEUE/FORM

QMS 1725 Print System

QMS

ESP

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General Linear Models Procedure
Class Level Information

Class	Levels	Values
SITE	8	1 2 3 4 5 6 7 8
SEX	2	1 2

Number of observations in data set = 149

General Linear Models Procedure

Dependent Variable: AS

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	4.23440097	0.28229340	12.01	0.0001
Error	133	3.12702831	0.02351149		
Corrected Total	148	7.36142928			

R-Square	C.V.	Root MSE	AS Mean
0.575215	24.54895	0.153335	0.624607

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	3.69378371	0.52768339	22.44	0.0001
SEX	1	0.01816014	0.01816014	0.77	0.3811
SITE*SEX	7	0.52245713	0.07463673	3.17	0.0039

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	3.68372426	0.52624632	22.38	0.0001
SEX	1	0.01806092	0.01806092	0.77	0.3824
SITE*SEX	7	0.52245713	0.07463673	3.17	0.0039

General Linear Models Procedure

Dependent Variable: PB

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	3.23847831	0.21589855	0.69	0.7862
Error	133	41.33260900	0.31077150		
Corrected Total	148	44.57108731			

R-Square	C.V.	Root MSE	PB Mean
0.072659	190.4238	0.557469	0.292752

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	2.54419002	0.36345572	1.17	0.3245
SEX	1	0.07926058	0.07926058	0.26	0.6144
SITE*SEX	7	0.61502770	0.08786110	0.28	0.9598

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	2.69449906	0.38492844	1.24	0.2862
SEX	1	0.14746562	0.14746562	0.47	0.4921
SITE*SEX	7	0.61502770	0.08786110	0.28	0.9598

General Linear Models Procedure

Level of SITE	N	AS Mean	AS SD	PB Mean	PB SD
1	20	0.64235000	0.15972024	0.53165000	1.15557852
2	20	0.80775000	0.11424207	0.23182500	0.31239690
3	20	0.68325000	0.18283783	0.11915000	0.06004496
4	20	0.67150000	0.11596846	0.14337500	0.10619605
5	21	0.74621429	0.17583363	0.37742857	0.65896651
6	15	0.35153333	0.22013141	0.27000000	0.39302326
7	13	0.68323077	0.11630144	0.38830769	0.38136212
8	20	0.35720000	0.17550097	0.30380000	0.31834103

Level of SEX	N	AS Mean	AS SD	PB Mean	PB SD
1	72	0.60848611	0.21411126	0.31238889	0.63636132
2	77	0.63968182	0.23142355	0.27438961	0.45545674

Level of SITE	Level of SEX	N	AS Mean	AS SD	PB Mean	PB SD
1	1	10	0.54330000	0.13264242	0.57740000	1.41255751
1	2	10	0.74140000	0.12024808	0.48590000	0.90505635
2	1	10	0.78300000	0.14043979	0.15595000	0.10072527
2	2	10	0.83250000	0.08042422	0.30770000	0.42788811
3	1	10	0.63900000	0.10295091	0.16630000	0.04377734
3	2	10	0.72750000	0.23584658	0.07200000	0.02747120
4	1	10	0.77920000	0.04827882	0.10845000	0.05429060
4	2	10	0.56380000	0.01687075	0.17830000	0.13472280
5	1	10	0.77030000	0.07980260	0.43540000	0.76860107
5	2	11	0.72431818	0.23451186	0.32472727	0.57479128
6	1	8	0.36762500	0.21372207	0.36437500	0.52924770
6	2	7	0.33314286	0.24297835	0.16214286	0.09049388
7	1	4	0.64525000	0.12434730	0.59125000	0.63407170
7	2	9	0.70011111	0.11596922	0.29811111	0.19401768
8	1	10	0.31410000	0.12177251	0.27770000	0.10693513
8	2	10	0.40030000	0.21463201	0.32990000	0.44832266

General Linear Models Procedure

Student-Newman-Keuls test for variable: AS

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 0.023511
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.100728	0.1207066	0.1324979	0.1408365

Number of Means	6	7	8
Critical Range	0.1472605	0.1524687	0.156838

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	0.80775	20	2
A			
B A	0.74621	21	5
B A			
B A	0.68325	20	3
B A			
B A	0.68323	13	7
B A			
B A	0.67150	20	4
B			
B	0.64235	20	1
C	0.35720	20	8
C			
C	0.35153	15	6

General Linear Models Procedure

Student-Newman-Keuls test for variable: PB

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 0.310771
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.3662103	0.4388455	0.4817143	0.5120304

Number of Means	6	7	8
Critical Range	0.5353857	0.5543209	0.570206

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	0.5316	20	1
A			
A	0.3883	13	7
A			
A	0.3774	21	5
A			
A	0.3038	20	8
A			
A	0.2700	15	6
A			
A	0.2318	20	2
A			
A	0.1434	20	4
A			
A	0.1192	20	3

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SITE	8	1 2 3 4 5 6 7 8

Number of observations in data set = 149

General Linear Models Procedure

Dependent Variable: AS

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	3.69378371	0.52768339	20.29	0.0001
Error	141	3.66764558	0.02601167		
Corrected Total	148	7.36142928			

R-Square	C.V.	Root MSE	AS Mean
0.501775	25.82124	0.161281	0.624607

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	3.69378371	0.52768339	20.29	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	3.69378371	0.52768339	20.29	0.0001

General Linear Models Procedure

Dependent Variable: PB

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	2.54419002	0.36345572	1.22	0.2960
Error	141	42.02689729	0.29806310		
Corrected Total	148	44.57108731			

R-Square	C.V.	Root MSE	PB Mean
0.057082	186.4896	0.545952	0.292752

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	2.54419002	0.36345572	1.22	0.2960

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	2.54419002	0.36345572	1.22	0.2960

General Linear Models Procedure

Student-Newman-Keuls test for variable: AS

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 0.026012
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.1058932	0.1268812	0.1392644	0.1480198

Number of Means	6	7	8
Critical Range	0.1547626	0.1602308	0.1648166

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	0.80775	20	2
A			
B A	0.74621	21	5
B A			
B A	0.68325	20	3
B A			
B A	0.68323	13	7
B A			
B A	0.67150	20	4
B			
B	0.64235	20	1
C	0.35720	20	8
C			
C	0.35153	15	6

General Linear Models Procedure

Student-Newman-Keuls test for variable: PB

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 0.298063
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.3584577	0.429504	0.4714222	0.5010599

Number of Means	6	7	8
Critical Range	0.5238851	0.5423952	0.5579187

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	0.5316	20	1
A			
A	0.3883	13	7
A			
A	0.3774	21	5
A			
A	0.3038	20	8
A			
A	0.2700	15	6
A			
A	0.2318	20	2
A			
A	0.1434	20	4
A			
A	0.1192	20	3

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SITE	8	1 2 3 4 5 6 7 8
SEX	2	1 2

Number of observations in data set = 149

General Linear Models Procedure

Dependent Variable: RAS RANK FOR VARIABLE AS

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	154248.1510	10283.2101	11.27	0.0001
Error	133	121378.8490	912.6229		
Corrected Total	148	275627.0000			

R-Square	C.V.	Root MSE	RAS Mean
0.559626	40.27953	30.20965	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	118791.9085	16970.2726	18.60	0.0001
SEX	1	2249.5495	2249.5495	2.46	0.1188
SITE*SEX	7	33206.6930	4743.8133	5.20	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	118638.5179	16948.3597	18.57	0.0001
SEX	1	2183.7570	2183.7570	2.39	0.1243
SITE*SEX	7	33206.6930	4743.8133	5.20	0.0001

General Linear Models Procedure

Dependent Variable: RPB RANK FOR VARIABLE PB

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	77456.73522	5163.78235	3.47	0.0001
Error	133	198167.76478	1489.98319		
Corrected Total	148	275624.50000			

R-Square	C.V.	Root MSE	RPB Mean
0.281023	51.46707	38.60030	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	52763.99698	7537.71385	5.06	0.0001
SEX	1	3180.86446	3180.86446	2.13	0.1463
SITE*SEX	7	21511.87378	3073.12483	2.06	0.0519

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	52233.90612	7461.98659	5.01	0.0001
SEX	1	3110.80225	3110.80225	2.09	0.1508
SITE*SEX	7	21511.87378	3073.12483	2.06	0.0519

General Linear Models Procedure

Level of SITE	N	RAS Mean	RAS SD	RPB Mean	RPB SD
1	20	73.500000	33.8199567	65.050000	46.4723744
2	20	113.400000	32.6228851	71.075000	39.7790857
3	20	84.300000	37.4813638	52.350000	38.0097287
4	20	76.925000	32.2556707	58.650000	39.7743967
5	21	102.380952	36.1275189	73.119048	48.3608583
6	15	29.666667	34.7597194	77.133333	47.5835606
7	13	78.461538	29.4777187	111.346154	23.6338252
8	20	29.875000	28.0745600	104.625000	21.8565147

Level of SEX	N	RAS Mean	RAS SD	RPB Mean	RPB SD
1	72	70.3819444	40.8614537	78.5138889	42.0789811
2	77	79.3181818	45.0306846	71.7142857	44.1571229

Level of SITE	Level of SEX	N	RAS Mean	RAS SD	RPB Mean	RPB SD
1	1	10	50.850000	21.8391214	62.750000	44.9185992
1	2	10	96.150000	28.2430424	67.350000	50.2980285
2	1	10	104.050000	38.3662540	66.300000	35.0936841
2	2	10	122.750000	24.0938558	75.850000	45.3688892
3	1	10	67.750000	26.1281564	83.450000	22.5898822
3	2	10	100.850000	40.9200100	21.250000	19.7572068
4	1	10	105.550000	18.0991866	48.300000	33.9298296
4	2	10	48.300000	6.9290051	69.000000	44.1644654
5	1	10	103.500000	27.5882423	80.400000	52.3905208
5	2	11	101.363636	43.8520757	66.500000	45.8917204
6	1	8	30.875000	31.9304490	80.437500	53.9691959
6	2	7	28.285714	40.3183758	73.357143	43.0558884
7	1	4	69.000000	26.7457162	120.250000	22.6182080
7	2	9	82.666667	31.1528490	107.388889	24.2638849
8	1	10	22.750000	15.0651364	111.650000	19.8046712
8	2	10	37.000000	36.3891009	97.600000	22.5077764

General Linear Models Procedure

Student-Newman-Keuls test for variable: RAS

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 912.6229
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	19.845206	23.781364	26.104456	27.747307

Number of Means	6	7	8
Critical Range	29.012946	30.039062	30.899886

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	113.40	20	2
A			
B A	102.38	21	5
B			
B C	84.30	20	3
B C			
B C	78.46	13	7
B C			
B C	76.93	20	4
C			
C	73.50	20	1
D	29.88	20	8
D			
D	29.67	15	6

General Linear Models Procedure

Student-Newman-Keuls test for variable: RPB

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 1489.983
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	25.35716	30.386576	33.354901	35.454048

Number of Means	6	7	8
Critical Range	37.071216	38.382333	39.482249

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	111.35	13	7
A			
A	104.63	20	8
B	77.13	15	6
B			
B	73.12	21	5
B			
B	71.08	20	2
B			
B	65.05	20	1
B			
B	58.65	20	4
B			
B	52.35	20	3

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SITE	8	1 2 3 4 5 6 7 8

Number of observations in data set = 149

General Linear Models Procedure

Dependent Variable: RAS RANK FOR VARIABLE AS

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	118791.9085	16970.2726	15.26	0.0001
Error	141	156835.0915	1112.3056		
Corrected Total	148	275627.0000			

R-Square	C.V.	Root MSE	RAS Mean
0.430988	44.46833	33.35125	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	118791.9085	16970.2726	15.26	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	118791.9085	16970.2726	15.26	0.0001

General Linear Models Procedure

Dependent Variable: RPB RANK FOR VARIABLE PB

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	52763.99698	7537.71385	4.77	0.0001
Error	141	222860.50302	1580.57094		
Corrected Total	148	275624.50000			

R-Square	C.V.	Root MSE	RPB Mean
0.191434	53.00853	39.75640	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	52763.99698	7537.71385	4.77	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	52763.99698	7537.71385	4.77	0.0001

General Linear Models Procedure

Student-Newman-Keuls test for variable: RAS

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 1112.306
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	21.897566	26.237664	28.798372	30.608892

Number of Means	6	7	8
Critical Range	32.003243	33.133997	34.0823

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	113.40	20	2
A			
B A	102.38	21	5
B			
B	84.30	20	3
B			
B	78.46	13	7
B			
B	76.93	20	4
B			
B	73.50	20	1
C	29.88	20	8
C			
C	29.67	15	6

General Linear Models Procedure

Student-Newman-Keuls test for variable: RPB

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 1580.571
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	26.103021	31.27664	34.329136	36.487368

Number of Means	6	7	8
Critical Range	38.149506	39.497423	40.627849

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	111.35	13	7
A			
B A	104.63	20	8
B			
B C	77.13	15	6
B C			
B C	73.12	21	5
B C			
B C	71.08	20	2
C			
C	65.05	20	1
C			
C	58.65	20	4
C			
C	52.35	20	3

JOB FLAG

SATURN::LEE_RB
Entry 630
APGDERLI

Liver data
Cr + Pb
Excluding #4, 5+6
but including #34's new data

User Information:	
User Name:	LEE_RB
Account:	DAKKRO
UIC:	LEE_RB
Rights List:	LEE_RB ([DAKKRO LEE_RB])
Submit:	
Queue:	PR$1129A_QMS
Priority:	100
Time:	28-NOV-1994 14:59:37.40
Print:	
Queue:	PR$1129A_QMS
Device:	QM1129::
Library:	SYS$LIBRARY:QMS$DEVCTL20.TLB
Form:	QMS$DEFAULT
Qualifiers:	/QUEUE/FORM

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141N 50105: 30 Nov 94 Robin Lee 5-193 [lee_rb: analysis of other liv
(Message # 141: 50105 bytes, New)
Date: Wed, 30 Nov 94 14:18:57 EST
From: Robin Lee 5-1939 <rlee@aeha1.apgea.army.mil>
To: jwhaley@aeha1.apgea.army.mil
Subject: [lee_rb: analysis of other liver data]

Janet, this is the print out from the analysis. Please disregard the title referring to outliers, since there are noe for arsenic, cadmium and mercury. I'll follow with a summary similar to the other one.
Robyn
----- Forwarded message # 1:

Received: from [131.92.62.17] by aeha1.apgea.army.mil id aa00198;
30 Nov 94 14:08 EST
Date: Wed, 30 Nov 1994 14:09:00 -0500
Message-Id: <94113014090026@mricd3.apgea.army.mil>
From: lee_rb@mricd3.apgea.army.mil
To: rlee@aeha1.apgea.army.mil
Subject: analysis of other liver data
X-VMS-To: SMTP%"rlee@aeha1.apgea.army.mil"
X-VMS-Cc: LEE_RB

1 TWO WAY ANOVA ON LIVER DATA 1
excluding outliers but new data for 34
14:00 Wednesday, November 30, 1994

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SITE	8	1 2 3 4 5 6 7 8
SEX	2	1 2

Number of observations in data set = 149

1 TWO WAY ANOVA ON LIVER DATA 2
excluding outliers but new data for 34
14:00 Wednesday, November 30, 1994

General Linear Models Procedure

Dependent Variable: AS

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	3.52711035	0.23514069	7.71	0.0001
Error	133	4.05555996	0.03049293		
Corrected Total	148	7.58267031			

R-Square	C.V.	Root MSE	AS Mean

0.465154	26.17064	0.174622		0.667245

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	2.84604994	0.40657856	13.33	0.0001
SEX	1	0.05302758	0.05302758	1.74	0.1895
SITE*SEX	7	0.62803283	0.08971898	2.94	0.0068

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	2.74492149	0.39213164	12.86	0.0001
SEX	1	0.03284474	0.03284474	1.08	0.3012
SITE*SEX	7	0.62803283	0.08971898	2.94	0.0068

General Linear Models Procedure

Dependent Variable: CD

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.86456368	0.05763758	3.40	0.0001
Error	133	2.25355038	0.01694399		
Corrected Total	148	3.11811406			

R-Square	C.V.	Root MSE	CD Mean
0.277271	100.1611	0.130169	0.129960

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	0.50460180	0.07208597	4.25	0.0003
SEX	1	0.15527654	0.15527654	9.16	0.0030
SITE*SEX	7	0.20468535	0.02924076	1.73	0.1081

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	0.48920676	0.06988668	4.12	0.0004
SEX	1	0.12073122	0.12073122	7.13	0.0085
SITE*SEX	7	0.20468535	0.02924076	1.73	0.1081

General Linear Models Procedure

Dependent Variable: HG

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	0.15960028	0.01064002	0.84	0.6360
Error	133	1.69220341	0.01272333		

Corrected Total	148	1.85180369			

R-Square	C.V.	Root MSE	HG Mean
0.086186	178.4168	0.112798	0.063221

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	0.08824113	0.01260588	0.99	0.4408
SEX	1	0.00239355	0.00239355	0.19	0.6652
SITE*SEX	7	0.06896560	0.00985223	0.77	0.6098

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	0.08747730	0.01249676	0.98	0.4470
SEX	1	0.00207216	0.00207216	0.16	0.6872
SITE*SEX	7	0.06896560	0.00985223	0.77	0.6098

General Linear Models Procedure

Level of SITE	N	AS Mean	AS SD	CD Mean	CD SD
1	20	0.72270000	0.13701867	0.06735500	0.07424568
2	20	0.81150000	0.16089143	0.22778500	0.23680265
3	20	0.70870000	0.14117704	0.19765500	0.19210557
4	20	0.58067500	0.14769459	0.11213500	0.11245566
5	21	0.70900000	0.12680655	0.09890952	0.09031175
6	15	0.45180000	0.31491613	0.09452000	0.09693849
7	13	0.90353846	0.10321145	0.17888462	0.11037930
8	20	0.47680000	0.25722090	0.07225000	0.05665680

Level of SITE	N	HG Mean	HG SD
1	20	0.05250000	0.01118034
2	20	0.05000000	0.00000000
3	20	0.05000000	0.00000000
4	20	0.12175000	0.28443515
5	21	0.07309524	0.10583568
6	15	0.05000000	0.00000000
7	13	0.05000000	0.00000000
8	20	0.05000000	0.00000000

Level of SEX	N	AS Mean	AS SD	CD Mean	CD SD
1	72	0.63786806	0.24242760	0.16140417	0.17218660
2	77	0.69471429	0.20805116	0.10055714	0.10731977

Level of SEX	N	HG Mean	HG SD

	1	72	0.06763889	0.14967094
	2	77	0.05909091	0.05833054

Level of SITE	Level of SEX	N	AS Mean	AS SD	CD Mean	CD SD
1	1	10	0.69990000	0.17218688	0.07344000	0.08256028
1	2	10	0.74550000	0.09397192	0.06127000	0.06883931
2	1	10	0.90380000	0.06531088	0.32324000	0.24818042
2	2	10	0.71920000	0.17734449	0.13233000	0.19115427
3	1	10	0.63090000	0.12895344	0.26950000	0.23725186
3	2	10	0.78650000	0.10952955	0.12581000	0.10075071
4	1	10	0.49685000	0.17194412	0.14430000	0.14568806
4	2	10	0.66450000	0.02952306	0.07997000	0.05633470
5	1	10	0.68290000	0.13383941	0.11130000	0.09247949
5	2	11	0.73272727	0.12139859	0.08764545	0.09122567
6	1	8	0.52975000	0.32340145	0.13975000	0.11108748
6	2	7	0.36271429	0.30335003	0.04282857	0.04104050
7	1	4	0.88800000	0.03741657	0.12862500	0.04843789
7	2	9	0.91044444	0.12361039	0.20122222	0.12478459
8	1	10	0.39930000	0.27406733	0.07708000	0.08028042

General Linear Models Procedure

Level of SITE	Level of SEX	N	AS Mean	AS SD	CD Mean	CD SD
8	2	10	0.55430000	0.22631053	0.06742000	0.01672914

Level of SITE	Level of SEX	N	HG Mean	HG SD
1	1	10	0.05000000	0.00000000
1	2	10	0.05500000	0.01581139
2	1	10	0.05000000	0.00000000
2	2	10	0.05000000	0.00000000
3	1	10	0.05000000	0.00000000
3	2	10	0.05000000	0.00000000
4	1	10	0.17700000	0.40160926
4	2	10	0.06650000	0.05217758
5	1	10	0.05000000	0.00000000
5	2	11	0.09409091	0.14623300
6	1	8	0.05000000	0.00000000
6	2	7	0.05000000	0.00000000
7	1	4	0.05000000	0.00000000
7	2	9	0.05000000	0.00000000
8	1	10	0.05000000	0.00000000
8	2	10	0.05000000	0.00000000

General Linear Models Procedure

Student-Newman-Keuls test for variable: AS

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 0.030493
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.1147122	0.1374645	0.1508928	0.1603891

Number of Means	6	7	8
Critical Range	0.1677049	0.1736362	0.1786121

Means with the same letter are not significantly different.

SNK Grouping		Mean	N	SITE
	A	0.90354	13	7
	A			
B	A	0.81150	20	2
B				
B	C	0.72270	20	1
B	C			
B	C	0.70900	21	5
B	C			
B	C	0.70870	20	3
	C			
D	C	0.58068	20	4
D				
D		0.47680	20	8
D				
D		0.45180	15	6

General Linear Models Procedure

Student-Newman-Keuls test for variable: CD

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 0.016944
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.0855102	0.1024705	0.1124804	0.1195592

Number of Means	6	7	8
Critical Range	0.1250127	0.129434	0.1331432

Means with the same letter are not significantly different.

SNK Grouping			Mean	N	SITE
	A		0.22779	20	2
	A				
B	A		0.19766	20	3
B	A				
B	A	C	0.17888	13	7
B		C			
B		C	0.11214	20	4
B		C			
B		C	0.09891	21	5
B		C			
B		C	0.09452	15	6
		C			
		C	0.07225	20	8
		C			
		C	0.06736	20	1

TWO WAY ANOVA ON LIVER DATA
excluding outliers but new data for 34
14:00 Wednesday, November 30, 1994

General Linear Models Procedure

Student-Newman-Keuls test for variable: HG

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 0.012723
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.0740987	0.0887956	0.0974697	0.1036038

Number of Means	6	7	8
Critical Range	0.1083295	0.1121608	0.115375

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	0.12175	20	4
A			
A	0.07310	21	5
A			
A	0.05250	20	1
A			
A	0.05000	15	6
A			
A	0.05000	13	7
A			
A	0.05000	20	2
A			
A	0.05000	20	3
A			

A 0.05000 20 8

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SITE	8	1 2 3 4 5 6 7 8
SEX	2	1 2

Number of observations in data set = 149

General Linear Models Procedure

Dependent Variable: RAS RANK FOR VARIABLE AS

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	129225.7182	8615.0479	7.83	0.0001
Error	133	146410.2818	1100.8292		
Corrected Total	148	275636.0000			

R-Square	C.V.	Root MSE	RAS Mean
0.468827	44.23833	33.17875	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	102769.2690	14681.3241	13.34	0.0001
SEX	1	1108.9867	1108.9867	1.01	0.3173
SITE*SEX	7	25347.4625	3621.0661	3.29	0.0029

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	99428.20464	14204.02923	12.90	0.0001
SEX	1	535.25691	535.25691	0.49	0.4868
SITE*SEX	7	25347.46252	3621.06607	3.29	0.0029

General Linear Models Procedure

Dependent Variable: RCD RANK FOR VARIABLE CD

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F

Model	15	55592.01701	3706.13447	2.27	0.0068
Error	133	216779.98299	1629.92468		
Corrected Total	148	272372.00000			

R-Square	C.V.	Root MSE	RCD Mean
0.204103	53.82977	40.37233	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	31468.75165	4495.53595	2.76	0.0104
SEX	1	10499.34681	10499.34681	6.44	0.0123
SITE*SEX	7	13623.91855	1946.27408	1.19	0.3105

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	28728.50431	4104.07204	2.52	0.0183
SEX	1	9096.55760	9096.55760	5.58	0.0196
SITE*SEX	7	13623.91855	1946.27408	1.19	0.3105

General Linear Models Procedure

Dependent Variable: RHG RANK FOR VARIABLE HG

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	15	1573.463636	104.897576	0.70	0.7846
Error	133	20036.536364	150.650649		
Corrected Total	148	21610.000000			

R-Square	C.V.	Root MSE	RHG Mean
0.072812	16.36531	12.27398	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	1063.307143	151.901020	1.01	0.4283
SEX	1	138.034390	138.034390	0.92	0.3402
SITE*SEX	7	372.122104	53.160301	0.35	0.9276

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	1045.091034	149.298719	0.99	0.4406
SEX	1	106.444418	106.444418	0.71	0.4021
SITE*SEX	7	372.122104	53.160301	0.35	0.9276

General Linear Models Procedure

Level of SITE	N	RAS Mean	RAS SD	RCD Mean	RCD SD
1	20	82.675000	34.7181414	54.450000	37.0958573
2	20	109.175000	34.2941130	85.925000	56.7782564
3	20	76.200000	35.6921781	92.225000	46.3597134
4	20	45.025000	17.2782758	72.275000	43.8221510
5	21	76.928571	27.9241319	69.023810	41.8391193
6	15	48.866667	53.2421915	65.766667	42.7454537
7	13	125.846154	14.2586006	103.384615	25.1496801
8	20	46.450000	45.8954475	64.875000	20.5226928

Level of SITE	N	RHG Mean	RHG SD
1	20	76.6500000	16.3232962
2	20	73.0000000	0.0000000
3	20	73.0000000	0.0000000
4	20	80.5000000	23.0867928
5	21	76.5714286	16.3663418
6	15	73.0000000	0.0000000
7	13	73.0000000	0.0000000
8	20	73.0000000	0.0000000

Level of SEX	N	RAS Mean	RAS SD	RCD Mean	RCD SD
1	72	70.2361111	46.5466578	82.6180556	44.8822005
2	77	79.4545455	39.5111728	67.8766234	39.9445467

Level of SEX	N	RHG Mean	RHG SD
1	72	74.0555556	8.9566859
2	77	75.8831169	14.4139680

Level of SITE	Level of SEX	N	RAS Mean	RAS SD	RCD Mean	RCD SD
1	1	10	77.400000	39.7343960	57.050000	38.7695829
1	2	10	87.950000	30.0660846	51.850000	37.2424862
2	1	10	130.550000	13.4090558	111.200000	48.4711827
2	2	10	87.800000	35.8850015	60.650000	55.1059837
3	1	10	55.200000	29.1920842	103.650000	48.3356609
3	2	10	97.200000	29.2785473	80.800000	43.7132068
4	1	10	32.350000	13.1488276	77.500000	53.4015189
4	2	10	57.700000	10.0172074	67.050000	33.7897503
5	1	10	72.750000	25.9938561	75.850000	41.7273225
5	2	11	80.727273	30.2996400	62.818182	42.9536219
6	1	8	61.000000	56.4832466	85.500000	44.3122041
6	2	7	35.000000	49.7158593	43.214286	29.3255536
7	1	4	129.250000	10.3400516	94.625000	19.7626542
7	2	9	124.333333	16.0156174	107.277778	27.3291409
8	1	10	36.950000	48.0500029	63.350000	27.6184821
8	2	10	55.950000	44.0166951	66.400000	11.0095918

General Linear Models Procedure

Level of SITE	Level of SEX	N	RHG Mean	RHG SD
1	1	10	73.0000000	0.0000000
1	2	10	80.3000000	23.0846269
2	1	10	73.0000000	0.0000000
2	2	10	73.0000000	0.0000000
3	1	10	73.0000000	0.0000000
3	2	10	73.0000000	0.0000000
4	1	10	80.6000000	24.0333102
4	2	10	80.4000000	23.4008547
5	1	10	73.0000000	0.0000000
5	2	11	79.8181818	22.6133508
6	1	8	73.0000000	0.0000000
6	2	7	73.0000000	0.0000000
7	1	4	73.0000000	0.0000000
7	2	9	73.0000000	0.0000000
8	1	10	73.0000000	0.0000000
8	2	10	73.0000000	0.0000000

General Linear Models Procedure

Student-Newman-Keuls test for variable: RAS

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 1100.829
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	21.795654	26.118669	28.670082	30.474397

Number of Means	6	7	8
Critical Range	31.864427	32.991393	33.936821

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	125.85	13	7
A			
A	109.18	20	2
B	82.68	20	1
B			
B	76.93	21	5
B			
B	76.20	20	3
C	48.87	15	6
C			
C	46.45	20	8
C			
C	45.03	20	4

General Linear Models Procedure

Student-Newman-Keuls test for variable: RCD

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 1629.925
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	26.521232	31.781534	34.886125	37.081638

Number of Means	6	7	8
Critical Range	38.773046	40.144352	41.294762

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	103.38	13	7
A			
B A	92.23	20	3
B A			
B A	85.93	20	2
B A			
B A	72.28	20	4
B A			
B A	69.02	21	5
B A			
B A	65.77	15	6
B A			
B A	64.88	20	8
B			
B	54.45	20	1

General Linear Models Procedure

Student-Newman-Keuls test for variable: RHG

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 133 MSE= 150.6506
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	8.0629772	9.6622125	10.60607	11.273549

Number of Means	6	7	8
Critical Range	11.78777	12.204674	12.554421

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	80.500	20	4
A			
A	76.650	20	1
A			
A	76.571	21	5
A			
A	73.000	20	2
A			
A	73.000	20	3
A			
A	73.000	15	6
A			
A	73.000	13	7
A			
A	73.000	20	8

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SITE	8	1 2 3 4 5 6 7 8

Number of observations in data set = 149

General Linear Models Procedure

Dependent Variable: AS

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	2.84604994	0.40657856	12.10	0.0001
Error	141	4.73662037	0.03359305		
Corrected Total	148	7.58267031			

R-Square	C.V.	Root MSE	AS Mean

0.375336	27.46878	0.183284		0.667245

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	2.84604994	0.40657856	12.10	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	2.84604994	0.40657856	12.10	0.0001

General Linear Models Procedure

Dependent Variable: CD

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	0.50460180	0.07208597	3.89	0.0007
Error	141	2.61351226	0.01853555		
Corrected Total	148	3.11811406			

R-Square	C.V.	Root MSE	CD Mean
0.161829	104.7596	0.136145	0.129960

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	0.50460180	0.07208597	3.89	0.0007

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	0.50460180	0.07208597	3.89	0.0007

General Linear Models Procedure

Dependent Variable: HG

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	0.08824113	0.01260588	1.01	0.4283
Error	141	1.76356256	0.01250754		
Corrected Total	148	1.85180369			

R-Square	C.V.	Root MSE	HG Mean
0.047651	176.8973	0.111837	0.063221

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	0.08824113	0.01260588	1.01	0.4283

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	0.08824113	0.01260588	1.01	0.4283

General Linear Models Procedure

Student-Newman-Keuls test for variable: AS

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 0.033593
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.1203396	0.1441909	0.1582634	0.1682133

Number of Means	6	7	8
Critical Range	0.175876	0.1820902	0.1873016

Means with the same letter are not significantly different.

SNK Grouping		Mean	N	SITE
	A	0.90354	13	7
	A			
B	A	0.81150	20	2
B				
B	C	0.72270	20	1
B	C			
B	C	0.70900	21	5
B	C			
B	C	0.70870	20	3
	C			
D	C	0.58068	20	4
D				
D		0.47680	20	8
D				
D		0.45180	15	6

General Linear Models Procedure

Student-Newman-Keuls test for variable: CD

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 0.018536
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.0893895	0.1071065	0.1175597	0.1249506

Number of Means	6	7	8
Critical Range	0.1306425	0.1352585	0.1391296

Means with the same letter are not significantly different.

SNK Grouping		Mean	N	SITE
	A	0.22779	20	2
	A			
B	A	0.19766	20	3
B	A			
B	A	0.17888	13	7
B	A			
B	A	0.11214	20	4
B				
B		0.09891	21	5
B				
B		0.09452	15	6
B				
B		0.07225	20	8
B				
B		0.06736	20	1

General Linear Models Procedure

Student-Newman-Keuls test for variable: HG

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 0.012508
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	0.0734293	0.087983	0.0965699	0.1026411

Number of Means	6	7	8
Critical Range	0.1073168	0.1111086	0.1142885

Means with the same letter are not significantly different.

SNK Grouping		Mean	N	SITE
	A	0.12175	20	4
	A			

A	0.07310	21	5
A			
A	0.05250	20	1
A			
A	0.05000	15	6
A			
A	0.05000	13	7
A			
A	0.05000	20	2
A			
A	0.05000	20	3
A			
A	0.05000	20	8

General Linear Models Procedure
Class Level Information

Class	Levels	Values
SITE	8	1 2 3 4 5 6 7 8

Number of observations in data set = 149

General Linear Models Procedure

Dependent Variable: RAS RANK FOR VARIABLE AS

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	102769.2690	14681.3241	11.97	0.0001
Error	141	172866.7310	1226.0052		
Corrected Total	148	275636.0000			

R-Square	C.V.	Root MSE	RAS Mean
0.372844	46.68581	35.01436	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	102769.2690	14681.3241	11.97	0.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	102769.2690	14681.3241	11.97	0.0001

General Linear Models Procedure

Dependent Variable: RCD RANK FOR VARIABLE CD

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	31468.75165	4495.53595	2.63	0.0138
Error	141	240903.24835	1708.53368		
Corrected Total	148	272372.00000			

R-Square	C.V.	Root MSE	RCD Mean
0.115536	55.11255	41.33441	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	31468.75165	4495.53595	2.63	0.0138

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	31468.75165	4495.53595	2.63	0.0138

General Linear Models Procedure

Dependent Variable: RHG RANK FOR VARIABLE HG

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	1063.307143	151.901020	1.04	0.4044
Error	141	20546.692857	145.721226		
Corrected Total	148	21610.000000			

R-Square	C.V.	Root MSE	RHG Mean
0.049204	16.09534	12.07150	75.00000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
SITE	7	1063.307143	151.901020	1.04	0.4044

Source	DF	Type III SS	Mean Square	F Value	Pr > F
SITE	7	1063.307143	151.901020	1.04	0.4044

General Linear Models Procedure

Student-Newman-Keuls test for variable: RAS

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 1226.005
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	22.989521	27.546045	30.234447	32.135251

Number of Means	6	7	8
Critical Range	33.599133	34.786274	35.781866

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	125.85	13	7
A			
A	109.18	20	2
B	82.68	20	1
B			
C B	76.93	21	5
C B			
C B	76.20	20	3
C			
C	48.87	15	6
C			
C	46.45	20	8
C			
C	45.03	20	4

General Linear Models Procedure

Student-Newman-Keuls test for variable: RCD

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 1708.534
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	27.139106	32.518078	35.691734	37.935631

Number of Means	6	7	8
Critical Range	39.663743	41.065161	42.240456

Means with the same letter are not significantly different.

SNK Grouping		Mean	N	SITE
	A	103.38	13	7
	A			
B	A	92.23	20	3
B	A			
B	A	85.93	20	2
B	A			
B	A	72.28	20	4
B	A			
B	A	69.02	21	5
B	A			
B	A	65.77	15	6
B	A			
B	A	64.88	20	8
B				
B		54.45	20	1

General Linear Models Procedure

Student-Newman-Keuls test for variable: RHG

NOTE: This test controls the type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha= 0.05 df= 141 MSE= 145.7212
WARNING: Cell sizes are not equal.
Harmonic Mean of cell sizes= 18.132

Number of Means	2	3	4	5
Critical Range	7.9258378	9.4967391	10.423589	11.078908

Number of Means	6	7	8
Critical Range	11.583594	11.992871	12.33611

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	SITE
A	80.500	20	4
A			
A	76.650	20	1
A			
A	76.571	21	5
A			
A	73.000	20	2
A			
A	73.000	20	3
A			
A	73.000	15	6
A			
A	73.000	13	7
A			
A	73.000	20	8

APPENDIX C

RISK ASSESSMENT METHODOLOGIES

APPENDIX C

RISK ASSESSMENT METHODOLOGY

The methodology selected for the risk assessment is U.S. Environmental Protection Agency (EPA) guidance developed for Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) sites, also known as "Superfund." The calculations result in a quantitative estimate of health risk based on the contaminant concentrations and the site exposure characteristics. Assessments conducted using Superfund guidance are based on the reasonable maximum exposure (RME) scenario. The RME is defined as the highest exposure that is reasonably expected to occur at the site. The methodology does not use the absolute worst-case scenario, but is, nevertheless, very conservative in the data that is selected for use and the exposure and risk factors that are incorporated into the assessment. The result of this is the production of risk numbers that generally over estimate health risk by several orders of magnitude. The risk assessment has six distinct steps which will be discussed below.

1. DATA COLLECTION. The collection of an environmental data base is the heart of any risk assessment. An early determination of the types of data that will be required to complete the risk assessment is essential. Items such as contaminant identities, environmental fate, transport, and persistence of contaminants, characteristics of the source, and contaminant concentrations in the key exposure pathways are required for a quality data base. As with risk assessment, data collection has certain key steps that must be accomplished.

a. Review of available information. The initial step in formulating data needs is to review the available information on the site characteristics (i.e., climate, topography, contaminant sources), hazardous substances to be monitored (i.e., explosives, metal, breakdown products), and identify potential exposure pathways.

b. Defining Background Sampling Needs. Background sampling is conducted to distinguish site-related contaminants from naturally occurring or other non-site-related levels of chemicals (i.e., industrial).

c. Preliminary Identification of Potential Human Exposure. This area of data collection involves determining the following: environmental media that may be contaminated and to which individuals may be exposed and/or through which chemicals may be transported to the potential receptors; areas of concern (i.e., locations where the environmental media is to be sampled); types of contaminants expected at the sampling sites and their environmental behavior, persistence, and accumulation; and

potential routes of contaminant transport through the environment.

d. Developing an Overall Strategy for Sample Collection. In developing a sampling strategy that will adequately address the questions the risk assessment is trying to answer the following factors must determined: sample size, sample location, and sample type.

e. Quality Assurance/Quality Control (QA/QC) Measures. The QA/QC issues that need to be addressed in the data collection plan are: sampling protocols, sample collection devices/equipment, QC samples, collection procedures, and sample preservation.

2. DATA EVALUATION. After all the environmental samples have been collected and analyzed, the data set that is produced must be evaluated to determine its suitability for incorporation in the risk assessment. To evaluate the data and prepare a data set for the risk assessment, the following must be accomplished: evaluate the analytical methods, evaluate the data with respect to QA/QC parameters (i.e., blanks, data qualifiers, quanification limits, holding times), evaluate tentatively identified compounds, compare potential site-related contamination with background, and evaluate the chemicals to be carried through the risk assessment.

3. EXPOSURE ASSESSMENT. The exposure assessment portion of the risk assessment attempts to estimate the type and magnitude of exposures to the chemicals of potential concern that are impacting the receptor populations. The exposure assessment consists of the following:

a. Characterization of the Exposure Setting. In this step the physical environment is characterized (i.e., climate, meteorology, soil type, topography) along with a characterization of the potentially exposed populations (i.e., location relative to the source, activity patterns, and sensitive subgroups).

b. Identification of Exposure Pathways. This step of the exposure assessment identifies the pathways (i.e., air, soil, food) by which the previously identified populations may be exposed. The determination of complete exposure pathways involves the following: identify contaminant release sources (i.e., production areas, disposal areas, etc.) and receiving media (i.e., soil, plants, animals); evaluate fate and transport in release media; identify exposure points (i.e., population contact points with contaminants) and exposure routes (i.e., ingestion, inhalation, and dermal contact);

c. Quantification of Exposure. In this step; the risk assessor quantifies the magnitude, frequency, and duration of

exposure for each identified pathway. This process occurs in two steps:

(1) Estimation of Exposure Concentrations. This step of the process involves determining the concentration of contaminants that will be contacted over the exposure period. Exposure concentrations can be estimated using sampling and analytical data (as will be done in this risk assessment) or using chemical transport and environmental fate modeling. The EPA methodology for Superfund uses the reasonable maximum exposure for each pathway. This value is the 95 percent upper confidence limit of the arithmetic average of the monitoring data for the pathway being evaluated. This methodology develops a conservative exposure concentration, while not using the maximum concentration detected which would not be reasonable.

(2) Calculation of Intakes. In this step of the exposure quantification the chemical specific exposures for each identified pathway are calculated. Exposure estimates are expressed in terms of the mass of substance in contact with the body per unit body weight per unit time (e.g., mg chemical per kg body weight per day, also expressed as mg/kg-day). Chemical intakes are calculated using equations that include variables for exposure concentration, contact rate, exposure frequency, exposure duration, body weight, and exposure averaging time. There is a different equation for each exposure pathway/route (i.e., ingestion of food, dermal contact with soil, inhalation of airborne chemicals, etc.).

4. TOXICITY ASSESSMENT. The purpose of the toxicity assessment is to determine the potential for each chemical of concern to cause adverse effects on the exposed populations. In addition, if possible, to ascertain the relationship between the extent of exposure to a contaminant and the increased likelihood and/or severity of adverse effects. The toxicity assessment is accomplished in two steps: hazard identification and dose-response. Hazard identification is the determination of whether exposure to a contaminant can cause an increase in the incidence of a particular health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans. Dose-response evaluation is the process of characterizing the relationship between the dose of the contaminant administered of received and the incidence of adverse health effects in the exposed populations. The types of data considered in toxicological assessments come from human epidemiologic studies and work place exposures, animal studies, and supporting metabolic/physiologic studies. The toxicity assessment is conducted for both carcinogenic and noncarcinogenic effects. When assessing carcinogenic effects the critical toxicity value is the slope factor which estimates the upper bound probability of a response (cancer) per unit intake of a chemical over a lifetime. Another important factor when assessing cancer risk is

the weight-of-evidence classification. This EPA system groups chemicals based on the available toxicity data as to their status as human carcinogens (i.e., human carcinogen, probable human carcinogen, etc.). For assessing noncarcinogenic effects the most often used critical toxicity value at Superfund sites is the reference dose (RfD). The RfD is an estimate (with uncertainty of an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a specified period of time. There are different RfDs for different periods of time [i.e., chronic (lifetime), subchronic (2 weeks to 7 years), etc.]. In addition to time periods for RfDs, both SFs and RfDs are derived for the specific route of exposure (i.e., inhalation and ingestion, no RfDs or SFs are available for the dermal route of exposure). The EPA has listed a hierarchy of sources for toxicity information used in Superfund risk assessments and these were used throughout this study.

5. RISK CHARACTERIZATION. The risk characterization is the final step in the baseline health risk assessment process. In this step the toxicity and exposure assessments are integrated into quantitative and qualitative expressions of risk. To characterize potential noncarcinogenic effects, comparisons are made between projected intakes of contaminants and toxicity values (RfDs). Potential carcinogenic effects (i.e., probabilities that an individual will develop cancer over a lifetime of exposure) are estimated from projected intakes and chemical-specific dose-response values (slope factors). In accordance with EPA guidelines, intakes for estimating carcinogenic effects are averaged over the receptor populations lifetime, while intakes for estimating noncarcinogenic effects are averaged over the actual exposure period.

a. Cancer Risk. Excess lifetime cancer risks are obtained by multiplying the intake rate at the exposure point of the contaminant by its cancer slope factor. Under the Superfund Program, the EPA has determined the acceptable range of excess cancer to be 1×10^{-4} to 1×10^{-6} (i.e., the probability of one excess cancer in a population of 10,000 to one excess cancer in a population of 1,000,000, respectively, under the conditions of exposure). The total cancer risk for a site is generally determined by adding the individual cancer risks for each chemical in the pathways and the summing the risk for all the pathways. If there are known synergistic and/or antagonistic relationships between carcinogens or specific target organs are involved these factors can be taken into account when determining cancer risk.

b. Noncancer Risk. Noncancer risks are obtained by dividing each chemicals daily intake by its RfD to obtain a hazard quotient. The RfD selected (i.e., chronic or subchronic) is

determined by the effected populations period of exposure. These hazard quotients (HQ) are summed for the various contaminants to obtain a hazard index (HI) for the pathway. The HIs for the various pathways are then combined and this represents the total noncancer risk for the site. Under the EPA Superfund Program a hazard index of unity (1) is considered the threshold of concern. As with cancer risk the combining of HIs and HQs can be modified by specific toxicological information such as mechanism of action or target organs/systems effected.

APPENDIX D

TOXICOLOGY PROFILE

ARSEN

TOXICITY SUMMARY
for
INORGANIC ARSENIC

April 1992

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EXECUTIVE SUMMARY

The toxicity of inorganic arsenic (As) depends on its valence state (-3, +3, or +5), and also on the physical and chemical properties of the compound in which it occurs. Trivalent (As^{+3}) compounds are generally more toxic than pentavalent (As^{+5}) compounds, and the more water soluble compounds are usually more toxic and more likely to have systemic effects than the less soluble compounds, which are more likely to cause chronic pulmonary effects if inhaled. One of the most toxic inorganic arsenic compounds is arsine gas (AsH_3). It should be noted that laboratory animals are generally less sensitive than humans to the toxic effects of inorganic arsenic. In addition, in rodents the critical effects appear to be immunosuppression and hepato-renal dysfunction, whereas in humans the skin, vascular system, and peripheral nervous system are the primary target organs.

Water soluble inorganic arsenic compounds are absorbed through the G.I. tract (>90%) and lungs; distributed primarily to the liver, kidney, lung, spleen, aorta, and skin; and excreted mainly in the urine at rates as high as 80% in 61 hr following oral dosing (U.S. EPA, 1984; ATSDR, 1989; Crecelius, 1977). Pentavalent arsenic is reduced to the trivalent form and then methylated in the liver to less toxic methylarsinic acids (ATSDR, 1989).

Symptoms of acute inorganic arsenic poisoning in humans are nausea, anorexia, vomiting, epigastric and abdominal pain, and diarrhea. Dermatitis (exfoliative erythroderma), muscle cramps, cardiac abnormalities, hepatotoxicity, bone marrow suppression and hematologic abnormalities (anemia), vascular lesions, and peripheral neuropathy (motor dysfunction, paresthesia) have also been reported (U.S. Air Force, 1990; ATSDR, 1989; Franzblau and Lilis, 1989; U.S. EPA, 1984; Armstrong et al., 1984; Hayes, 1982; Mizuta et al., 1956). Oral doses as low as 20-60 g/kg/day have been reported to cause toxic effects in some individuals (ATSDR, 1989). Severe exposures can result in acute encephalopathy, congestive heart failure, stupor, convulsions, paralysis, coma, and death. The acute lethal dose to humans has been estimated to be about 0.6 mg/kg/day (ATSDR, 1989). General symptoms of chronic arsenic poisoning in humans are weakness, general debility and lassitude, loss of appetite and energy, loss of hair, hoarseness of voice, loss of weight, and mental disorders (Hindmarsh and McCurdy, 1986). Primary target organs are the skin (hyperpigmentation and hyperkeratosis) [Terada et al. 1960; Tseng et al., 1968; Zaldivar 1974; Cebrian et al., 1983; Huang et al., 1985], nervous system (peripheral neuropathy) [Hindmarsh et al., 1977, 1986; Valentine et al., 1982; Heyman et al., 1956; Mizuta et al., 1956; Tay and Seah, 1975], and vascular system [Tseng et al., 1968; Borgano and Greiber, 1972; Salcedo et al., 1984; Wu et al., 1989; Hansen, 1990]. Anemia, leukopenia, hepatomegaly, and portal hypertension have also been reported (Terada et al., 1960; Viallet et al., 1972; Morris et al., 1974; Datta, 1976). In addition, possible reproductive effects include a high male to female birth ratio (Lyster, 1977).

In animals, acute oral exposures can cause gastrointestinal and neurological effects (Heywood and Sortwell, 1979). Oral LD_{50} values range from about 10 to 300 mg/kg (ASTDR, 1989; U.S. Air Force, 1990). Low subchronic doses can result in immunosuppression, (Blakely et al., 1980) and hepato-renal effects (Mahaffey et al., 1981; Brown et al., 1976; Woods and Fowler, 1977, 1978; Fowler and Woods, 1979; Fowler et al., 1979). Chronic exposures have also resulted in mild hyperkeratosis and bile duct enlargement with hyperplasia, focal necrosis, and fibrosis (Baroni et al., 1963; Byron et al., 1967). Reduction in litter size, high male/female birth ratios, and fetotoxicity without significant fetal abnormalities occur following oral exposures (Schroeder and Mitchener, 1971; Hood et al., 1977; Baxley et al., 1981); however, parenteral dosing has resulted in exencephaly, encephaloceles, skeletal defects, and urogenital system abnormalities (Ferm and Carpenter, 1968; Hood and Bishop, 1972; Beaudoin, 1974; Burk and Beandoin, 1977).

The Reference Dose for chronic oral exposures, 0.0003 mg/kg/day, is based on a NOAEL of 0.0008 mg/kg/day and a LOAEL of 0.014 mg/kg/day for hyperpigmentation, keratosis, and possible vascular complications in a human population consuming arsenic-contaminated drinking water (U.S. EPA, 1991a). Because of uncertainties in the data, U.S. EPA (1991a) states that "strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value." The subchronic Reference Dose is the same as the chronic RfD, 0.0003 mg/kg/day (U.S. EPA, 1992).

Acute inhalation exposures to inorganic arsenic can damage mucous membranes, cause rhinitis, pharyngitis and laryngitis, and result in nasal septum perforation (U.S. EPA, 1984). Chronic inhalation

exposures, as occurring in the workplace, can lead to rhino-pharyno-laryngitis, tracheobronchitis, (Lundgren, 1954); dermatitis, hyperpigmentation, and hyperkeratosis (Perry et al., 1948; Pinto and McGill, 1955); leukopenia (Kyle and Pease, 1965; Hinc et al., 1977); peripheral nerve dysfunction as indicated by abnormal nerve conduction velocities (Feldman et al., 1979; Blom et al., 1985; Landau et al., 1977); and peripheral vascular disorders as indicated by Raynaud's syndrome and increased vasospastic reactivity in fingers exposed to low temperatures (Lagerkvist et al., 1986). Higher rates of cardiovascular disease have also been reported in some arsenic-exposed workers (Lee and Fraumeni, 1969; Axelson et al., 1978; Wingren and Axelson, 1985). Possible reproductive effects include a high frequency of spontaneous abortions and reduced birth weights (Nordström et al., 1978a,b). Arsine gas (AsH_3), at concentrations as low as 3-10 ppm for several hours, can cause toxic effects. Hemolysis, hemoglobinuria, jaundice, hemolytic anemia, and necrosis of the renal tubules have been reported in exposed workers (ACGIH, 1986; Fowler and Weissberg, 1974).

Animal studies have shown that inorganic arsenic, by intratracheal instillation, can cause pulmonary inflammation and hyperplasia (Webb et al., 1986, 1987), lung lesions (Pershagen et al., 1982), and immunosuppression (Hatch et al. (1985). Long-term inhalation exposures have resulted in altered conditioned reflexes and CNS damage (Rozenshstein, 1970). Reductions in fetal weight and in the number of live fetuses, and increases in fetal abnormalities due to retarded osteogenesis have been observed following inhalation exposures (Nagymajtenyi et al., 1985).

Subchronic and chronic RfCs for inorganic arsenic have not been derived.

Epidemiological studies have revealed an association between arsenic concentrations in drinking water and increased incidences of skin cancers (including squamous cell carcinomas and multiple basal cell carcinomas), as well as cancers of the liver, bladder, respiratory and gastrointestinal tracts (U.S. EPA, 1987; IARC, 1987; Sommers et al., 1953; Reymann et al., 1978; Dobson et al., 1965; Chen et al., 1985, 1986). Occupational exposure studies have shown a clear correlation between exposure to arsenic and lung cancer mortality (IARC, 1987; U.S. EPA, 1991a). U.S. EPA (1991a) has placed inorganic arsenic in weight-of-evidence group A, human carcinogen. A drinking water unit risk of 5E-5$(\mu g/L)^{-1}$ has been proposed (U.S. EPA, 1991a); derived from drinking water unit risks for females and males that are equivalent to slope factors of 1.0E-3 $(\mu g/kg/day)^{-1}$ (females) and 2.0E-3 $(\mu g/kg/day)^{-1}$ (males) (U.S. EPA, 1987). For inhalation exposures, a unit risk of 4.3E-3 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1991a) and a slope factor of 5.0E+1 $(mg/kg/day)^{-1}$ have been derived (U.S. EPA, 1992).

1. INTRODUCTION

The toxicity of inorganic compounds containing arsenic depends on the valence or oxidation state of the arsenic (-3, +3, or +5), as well as on the physical and chemical properties of the compound in which it occurs. Trivalent (As^{+3}) compounds such as arsenic trioxide (As_2O_3), arsenic trisulfide (As_2S_3), and sodium arsenite ($NaAsO_2$), are generally more toxic than pentavalent (As^{+5}) compounds such as arsenic pentoxide (As_2O_5), sodium arsenate (Na_2HAsO_4), and calcium arsenate ($Ca_3(AsO_4)_2$). Trivalent arsenic interacts with sulfhydryl groups of proteins and enzymes; pentavalent arsenic substitutes for phosphate groups important in oxidative phosphorylation (Squibb and Fowler, 1983). The relative toxicity of the trivalent and pentavalent forms may also be affected by factors such as the water solubility of the compound. Although the more water soluble arsenic compounds are generally more toxic and more likely to have systemic effects, the less soluble compounds are more likely to cause chronic pulmonary effects if inhaled. One of the most toxic arsenic compounds is arsine gas (AsH_3) with arsenic in the -3 valence state.

It should be noted that laboratory animals are generally less sensitive than humans to the toxic effects of inorganic arsenic. In addition, in rodents the critical effects appear to be immunosuppression and hepato-renal dysfunction, whereas in humans the skin, vascular system, and peripheral nervous system are the primary target organs.

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

Absorption of water soluble inorganic arsenic compounds through the G.I. tract is very high. In humans, absorption rates of 96.5% for trivalent sodium arsenite and 94% for soluble pentavalent arsenic have been reported (Bettley and O'Shea, 1975; Pomroy et al., 1980). In contrast, G.I. absorption of the less soluble arsenic trisulfide and lead arsenate was reported to be only 20-30% in hamsters (Marafante and Vahter, 1987). In tests on humans, absorption of the insoluble arsenic selenide appeared to be neglible as indicated by the absence of an increase in urinary arsenic excretion (Mappes, 1977).

Absorption of arsenic in the lungs is dependant on particle size as well as water solubility; respirable particles (0.1-1 μ) are carried further into the lungs and are therefore more likely to be absorbed (ATSDR, 1989). Estimates of pulmonary absorption may be complicated by the fact that some of the particles may be cleared from the lungs, then swallowed and absorbed through the G.I. tract. In studies on smelter workers exposed to arsenic dusts of about 5 μ particle size, Lagerkvist et al. (1986) estimated that 75% of the dust would be deposited in the respiratory tract and 80% of this would be absorbed directly or through the stomach after mucocillary clearance.

2.2. DISTRIBUTION

Following absorption of trivalent or pentavalent arsenic compounds, arsenic is initially accumulated in the liver, kidney, lung, spleen, aorta, and skin. With the exception of the skin, clearance from these organs is rapid. Arsenic is also extensively deposited in the hair and nails (U.S. EPA, 1984).

2.3. METABOLISM

Arsenic compounds are subject to metabolic transformation. In both humans and animals, pentavalent arsenic compounds are reduced to trivalent forms and then methylated in the liver to less toxic methylarsinic acids (ATSDR, 1989).

2.4. EXCRETION

Arsenic is cleared from the body relatively rapidly and primarily in the urine. Urinary excretion rates of 80% in 61 hr following oral doses and 30-80% in 4-5 days following parenteral doses have been measured in humans (Crecelius, 1977; Hunter et al., 1942). Arsenic is also lost from the body in the hair and nails, since this represents a non-biologically available arsenic pool.

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Common symptoms of inorganic arsenic poisoning are nausea, anorexia, vomiting, epigastric and abdominal pain, and diarrhea. Dermatitis (exfoliative erythroderma), muscle cramps, cardiac abnormalities, hepatotoxicity, bone marrow suppression and hematologic abnormalities (anemia and leukopenia), vascular lesions, and peripheral neuropathy (motor dysfunction, long axon Wallerian degeneration) have also been reported (U.S. Air Force, 1990; ATSDR, 1989; Franzblau and Lilis, 1989; U.S. EPA, 1984; Armstrong et al., 1984; Hayes, 1982; Mizuta et al., 1956).

Oral doses as low as 20-60 g/kg/day have been reported to cause toxic effects in some individuals (ATSDR, 1989). Severe exposures can result in acute encephalopathy, congestive heart failure, stupor, convulsions, paralysis, coma, and death. The acute lethal dose to humans has been estimated to be about 0.6 mg/kg/day (ATSDR, 1989). A dose estimated at 3 mg/day for a 1-2 month period was fatal to 1% of a group of infants receiving arsenic-contaminated milk (Hamamoto, 1955).

3.1.1.2. Animal

Monkeys exposed to acutely toxic doses of inorganic arsenic exhibit gastrointestinal distress and neurological effects. Adolescent and infant Rhesus monkeys receiving 5 daily oral doses of a complex inorganic arsenic compound containing the equivalent of 7.5 mg/kg of arsenic trioxide exhibited loss of condition, vomiting, diarrhea, salivation and uncontrolled shaking of the head (Heywood and Sortwell, 1979).

LD_{50} values for inorganic arsenic compounds in laboratory animals range from about 10 to 300 mg/kg (ASTDR, 1989; U.S. Air Force, 1990).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

Depending on the dose and duration, subchronic exposures to inorganic arsenic can cause toxic effects similar to those caused by acute and/or chronic exposures. Skin and vascular disorders, neuropathy, gastroenteritis, hepatotoxicity, and hematological abnormalities (anemia and leukopenia) have been reported in individuals exposed for time periods ranging from less than 6 months to 15 years (ATSDR, 1989; Huang et al., 1985).

Borgono and Greiber (1972) reported a 12% incidence of skin abnormalities in children whose drinking water contained 0.6-0.8 mg As/L. The earliest cases occurred about 4-5 years after the initial exposure. Cardiovascular effects, including Raynaud's syndrome, acrocyanosis, angina pectoris, hypertension, myocardial infarction, mesenteric thrombosis, systemic occlusive arterial disease, bronchiectasis, and recurrent broncho-pneumonia were also observed in this group of subjects (Zaldivar, 1980). The bronchiectasis and recurrent broncho-pneumonia were attributed to an immunosuppressive action of arsenic in the lungs. A significant decrease in the incidence of skin abnormalities was observed following a reduction in drinking water concentration to about 0.04 mg/L. After 4 years at the lower exposure, effects were rarely seen in children younger than 12 years old (Borgono et al., 1977).

Central nervous system deficits (hearing loss, eye damage, abnormal EEGs, mental retardation, epilepsy), electrocardiographic changes (elevated ST wave and extended QT interval), and skin abnormalities (melanosis, desquamation, rashes, and hyperkeratosis) occurred in infants who had been fed arsenic-contaminated milk for 1-2 months (Hamamoto, 1955). It was estimated that the daily arsenic intake was about 3 mg/day (U.S. EPA, 1984).

3.1.2.2. Animal

Immunosuppression and hepato-renal toxicity have been identified as toxic effects in rodents. Immunosuppression, as measured by hemagglutination, radial immunodiffusion, and Cunningham plaque assays, was observed in mice exposed for 3 weeks to sodium arsenite levels of 0.5 ppm in drinking water (Blakely et al., 1980). Reported hepato-renal effects include: (1) mild swelling of renal tubular cell mitochondria and decreases in liver-derived serum enzymes (aspartate aminotransferase [AST] and alkaline phosphatase) in rats following 10 weeks exposure to 50 ppm dietary arsenate (Mahaffey et al., 1981); (2) functional and ultrastructural changes in the kidneys of rats exposed for 6 weeks to arsenate concentrations of 85 and 125 ppm in drinking water (Brown et al., 1976); (3) disruption of liver biosynthesis of heme and -aminolevulinic (ALA) synthetase activity in mice and rats exposed for 6 wk to 40 and 85 ppm arsenic in drinking water (Woods and Fowler, 1977, 1978); (4) alteration of hepatocyte mitochondrial structure and liver enzyme activity (monoamine oxidase, cytochrome oxidase) in rats and mice exposed for 6 weeks to 20-85 ppm sodium arsenate in drinking water (Fowler and Woods, 1979; Fowler et al., 1979); and (5) increases in serum AST and alanine aminotransferase (ALT) levels due to hepatocyte plasma membrane dysfunction in beagle dogs fed dietary levels of sodium arsenite equivalent to 4 mg/kg for 58 days followed by 8 mg/kg/day for an additional 125 days (Neiger and Osweiler, 1989).

In a six-month study in which rats were fed 250 ppm pentavalent or trivalent arsenic, Douglas and Blendermann (1961) found that trivalent arsenic caused bile duct lesions and a significant depression in growth.

Although arsenic-induced skin disorders are not commonly seen in rodents, eczema, hyperplasia, and hyperkeratosis were reported in two-week-old rats dosed for 40 days by stomach intubation with 2 mg/kg/day or 10 mg/kg/day of arsenic trioxide (Ishinishi et al., 1976). Avoidance conditioning responses were also impaired by these dose levels (Osato, 1977).

3.1.3. Chronic Toxicity

3.1.3.1. Human

General symptoms of chronic arsenic poisoning are weakness, general debility and lassitude, loss of appetite and energy, loss of hair, hoarseness of the voice, loss of weight, and mental abnormalities

(Hindmarsh and McCurdy, 1986). Skin, neurological, and vascular disorders are the most common effects seen following long-term exposures.

Skin abnormalities, particularly hyperpigmentation and hyperkeratosis have been observed in populations exposed to arsenic in drinking water (Terada et al. 1960; Tseng et al., 1968; Zaldivar 1974; Cebrian et al., 1983; Huang et al., 1985). Tseng et al. (1968) reported an incidence rate of 18% for hyperpigmentation and 7% for hyperkeratosis in a Taiwanese population whose drinking water contained an average arsenic concentration of 0.4-0.6 ppm. Skin abnormalities were also reported in 40% of patients consuming Fowler's solution for 6-26 years (Fierz, 1965).

Arsenic-induced neurotoxicity is manifested as a peripheral neuropathy involving both sensory and motor nerves, and resulting in numbness and paresthesia, diminished sensations of touch, pain, heat, and cold, and muscle weakness (Hindmarsh et al., 1977; Hindmarsh and McCurdy, 1986; Valentine et al., 1982; Heyman et al., 1956; Mizuta et al., 1956; Tay and Seah, 1975).

Peripheral vascular disorders have been reported in several populations whose drinking water contained high arsenic levels (Tseng et al., 1968; Saleedo et al., 1984; Chen et al., 1988). Blackfoot disease (a condition caused by arteriosclerosis and thromboangiitis obliterans), which can result in gangrene of the lower extremities, occurred in 0.9% of one such population (Tseng et al., 1968; 1977). Epidemiological studies and mechanistic considerations have implicated arsenic as a possible causative factor in arteriosclerotic plaque formation and cardiovascular disease (Wu et al., 1989; Hansen, 1990; Penn, 1990).

Chronic oral exposures to arsenic reportedly have also resulted in anemia, leukopenia, liver swelling, and noncirrhotic portal hypertension (Terada et al., 1960; Vialle et al., 1972; Morris et al., 1974; Datta, 1976; Nevens et al., 1990).

3.1.3.2. Animal

Studies in rats have demonstrated no-adverse-effect levels of 1.4 (males) and 1.6 mg As/kg/day (females) for sodium arsenite and 2.8 (males) and 3.25 mg As/kg/day (females) for sodium arsenate (Byron et al., 1967). Similar studies on dogs revealed a no-adverse-effect level at 1.1 mg As/kg/day. A drinking water concentration of 5 ppm produced no toxic effects in rats when administered over an entire lifetime (Schroeder et al., 1968).

Mild hyperkeratosis has been reported in mice exposed for a lifetime to arsenic oxide in drinking water at a concentration of 0.01% (Baroni et al., 1963).

Bile duct enlargement with hyperplasia of the glandular elements, focal necrosis, and fibrosis was seen in rats receiving dietary arsenic levels of 125 and 250 ppm as sodium arsenite and 250 and 400 ppm as sodium arsenate for up to two years (Byron et al., 1967). Lifetime (29 mo) exposure to lead arsenate at a dietary level of 1850 ppm also caused bile duct lesions in rats (Kroes et al., 1974).

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

A high male-to-female birth ratio (157 to 100) was reported for a population that may have been exposed to elevated arsenic levels in their drinking water 10 to 11 months earlier (Lyster, 1977).

3.1.4.2. Animal

Chronic exposure of pregnant mice to 5 ppm sodium arsenite in drinking water resulted in a slight reduction in litter size and a higher male/female ratio (increased from 0.93 to 1.71), but no adverse effects on fetal development (Schroeder and Mitchner, 1971). Oral doses as high as 120 mg/kg/day of sodium arsenate were reported to be fetotoxic but not teratogenic to rats (Hood et al., 1977). Oral doses of 25-40 mg/kg of sodium arsenite caused prenatal mortality and a low, but non-significant, incidence of fetal malformations (exencephaly) in mice (Baxley et al., 1981).

3.1.5. Reference Dose

3.1.5.1. Subchronic

ORAL RfD: 0.0003 mg/kg/day (U.S. EPA, 1992)
UNCERTAINTY FACTOR: 3
NOAEL: 0.0008 mg/kg/day, epidemiological study.

COMMENT: The same study applies to the subchronic and chronic RfD (see Section 3.1.5.2).

3.1.5.2. Chronic

ORAL RfD: 0.0003 mg/kg/day (U.S. EPA, 1991a)
UNCERTAINTY FACTOR: 3
MODIFYING FACTOR: 1
NOAEL: 0.0008 mg/kg/day, epidemiological study
CONFIDENCE:
Study: Medium
Data Base: Medium
RfD: Medium

VERIFICATION DATE: 11/15/90

PRINCIPAL STUDIES: Tseng, W.P. 1977; Tseng et al., 1968

COMMENT: The NOAEL was based on an arithmetic mean of 0.009 mg/L in drinking water (range 0.001-0.17 mg/L), a daily water consumption of 4.5 L, and an arsenic intake in food of 0.002 mg/day. A LOAEL of 0.014 mg/kg/day for hyperpigmentation, keratosis, and possible vascular complications, was based on an arithmetic mean of 0.14 mg/L in drinking water (4.5 L/day), and 0.002 mg/kg in food. The UF of 3 is to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals.

NOTE: U.S. EPA (1991a) states that "strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1-0.8 g/kg/day"; therefore, considerable flexibility is allowed in formulating regulatory decisions.

3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

3.2.1.1. Human

Inorganic arsenic dusts can cause respiratory irritation and mucous membrane damage leading to rhinitis, pharyngitis or laryngitis. Several weeks exposure to high concentrations can result in nasal septum perforation (U.S. EPA, 1984). Although inhalation exposures to most inorganic arsenic compounds are not usually associated with acute lethality (ATSDR, 1989); exposure to 250 ppm of arsine gas is instantly fatal and several hours exposure to concentrations as low as 10 ppm can produce toxic symptoms and may also be fatal (Fowler and Weissberg, 1974; NIOSH, 1979). Arsine causes severe hemolysis, hemoglobinuria, jaundice, hemolytic anemia, and necrosis of the renal tubules (ACGIH, 1986; Fowler and Weissberg, 1974).

3.2.1.2. Animal

Intratracheal instillation studies indicate that inorganic arsenic can have direct toxic effects on respiratory tissue. Trivalent arsenic oxide and gallium arsenide were shown to cause pulmonary inflammation and hyperplasia in rats (Webb et al., 1986, 1987), and calcium arsenate caused lung lesions in

hamsters; however, arsenic trioxide and arsenic trisulfide did not have such an effect (Pershagen et al., 1982).

The pulmonary immune response can be affected by inorganic arsenic compounds. Hatch et al. (1985) reported significant increases in mortality of mice due to infectious streptococcal challenge following intratracheal injection of sodium arsenite, and Aranyi et al. (1985) reported similar increases in mortality as well as decreases in pulmonary bactericidal activity to *Klebsiella pneumonia* following single and multiple inhalation exposures to arsenic trioxide.

Exposure of mice to arsine concentrations as low as 2.5 ppm caused significant decreases in red blood cells, hematocrit and hemoglobin, as well as significant increases in white blood cell counts, and mean corpuscular volume of RBC. Erythropoiesis in bone marrow cells was impaired and erythropoiesis in the spleen was increased (Hong et al., 1989).

3.2.2. Subchronic Toxicity

3.2.2.1. Human

Subchronic inhalation exposures to inorganic arsenic are expected to cause toxic effects similar to those resulting from chronic exposures (see Section 3.2.3).

3.2.2.2. Animal

Rats exposed for 3 months to 46 g/m^3 of arsenic trioxide aerosol exhibited altered conditioned reflexes and CNS damage as evidenced by pericellular edema and neuronal cytolysis in the brain (Rozenshstein, 1970).

Rats exposed to 0.025 ppm arsine gas for 90 days developed anemia (Blair et al., 1990). Higher exposure levels (primarily 2.5 ppm) resulted in bone marrow hyperplasia, increased splenic hemosiderosis and extramedullary hematopoiesis, decreased packed cell volume, increased delta-aminolevulinic acid dehydratase activity, and increased relative spleen weight. Similar effects were seen in mice and hamsters.

3.2.3. Chronic Toxicity

3.2.3.1. Human

Information on the inhalation toxicity of inorganic arsenic is derived primarily from occupational exposure studies, particularly those involving smelter workers. Early studies identified chronic respiratory diseases (rhinitis, pharyngitis, laryngitis, tracheobronchitis, and pulmonary insufficiency) and blood disorders (leukopenia) in exposed workers (Lundgren, 1954; Kyle and Pease, 1965). In one study, a 23% incidence of relative neutropenia occurred in 130 smelter workers exposed to arsenic air concentrations averaging less than 0.5 mg/m^3 (Hine et al., 1977).

Neurological disorders (peripheral nerve dysfunction indicated by abnormal nerve conduction velocities) have been documented in smelter workers exposed to arsenic concentrations of 0.5 mg/m^3 (Feldman et al., 1979; Blom et al., 1985; Landau et al., 1977). Chronic encephalopathy, evidenced by cognitive impairment and psychological symptoms was reported in two workers exposed to arsenic fumes for 14-18 months (Morton and Caron, 1989). Abnormal electromyograms were reported for populations living near an arsenic mine and smelter (Takahashi, 1974). Hearing losses have been reported in children living near a coal-fired power plant burning high-arsenic content coal (U.S. EPA, 1984).

Chronic exposure of smelter workers to low levels of atmospheric arsenic (0.5 mg/m^3) caused subtle changes in the peripheral vascular system, as indicated by an increased incidence of Raynaud's syndrome (white fingers) and increased vasospastic reactivity in fingers exposed to low temperatures (Lagerkvist et al., 1986). Higher rates of cardiovascular disease have also been reported in some arsenic-exposed workers (Lee and Fraumeni, 1969; Axelson et al., 1978; Wingren and Axelson, 1985).

Dermatitis, hyperpigmentation, and hyperkeratosis were observed in early studies of workers exposed to inorganic arsenic (Perry et al., 1948; Pinto and McGill, 1953); however, it is not known to

what degree the reported effects were due to direct skin contact and accidental ingestion of the arsenic dust.

Chronic exposure to very low levels of arsine gas may have a cumulative effect in causing anemia (Fowler and Weissberg, 1974).

3.2.3.2 Animal

Glaser et al. (1986) exposed male Wistar rats to aerosols (<0.3 m MMAD) of arsenic trioxide for 18 months at concentrations of 0, 60, and 200 g/m^3. The animals were observed for one year after the termination of the exposures and no adverse effects on body weight, hematology, clinical chemistry, or macro- or microscopic structure of internal organs were reported.

3.2.4. Developmental and Reproductive Toxicity

3.2.4.1. Human

A significantly higher frequency of spontaneous abortions (11% vs 7.6%) and significantly reduced birth weights were recorded for a population living near a copper smelter when compared with control populations (Nordström et al., 1978a,b).

3.2.4.2. Animal

Nagymajtenyi et al. (1985) exposed mice for 4 hr/day to an aerosol of arsenic trioxide (28.5 mg/m^3) on days 9-12 of gestation, and found a significant reduction in fetal weight and in the number of live fetuses. In addition, there was a significant increase in the number of fetuses with retarded osteogenesis and an increase in the frequency of chromosomal aberrations (chromosome breaks and chromatid exchanges). Concentrations of 2.9 mg/m^3 and 0.26 mg/m^3 caused no significant changes, except a slight decrease in fetal weight.

3.2.5. Reference Dose/Concentration

Subchronic and chronic RfCs for inorganic arsenic have not been derived.

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

3.3.1.1. Human

Information on the acute toxicity of inorganic arsenic to humans by other routes of exposure was not available.

3.3.1.2. Animal

Intraperitoneal LD_{50} values of 4-20 mg/kg for various inorganic arsenic compounds have been reported (ATSDR, 1989).

3.3.2. Subchronic Toxicity

3.3.2.1. Human

Information on the subchronic toxicity of inorganic arsenic to humans by other routes of exposure was not available.

3.3.2.2. Animal

Intraperitoneal injections of sodium arsenate solution at a dose level of 0.2 mg/kg for two months, resulted in inner ear damage and hearing loss in guinea pigs (Aly et al., 1975).

3.3.3. Chronic Toxicity

3.3.3.1. Human

Skin contact with inorganic arsenic dusts in occupationally exposed workers has been associated with direct dermatitis, allergenic hypersensitivity, and conjunctivitis (U.S. EPA, 1984; Pinto and McGill, 1953; Holmqvist, 1951).

3.3.3.2. Animal

Weekly injections of up to 10 mg/kg/day, for 18 months did not produce signs of neuropathy in rats (Schaumburg, 1980).

3.3.4. Developmental and Reproductive Toxicity

3.3.4.1. Human

Information on the developmental and reproductive toxicity of inorganic arsenic to humans by other routes of exposure was not available.

3.3.4.2. Animal

Some inorganic arsenic compounds cause teratogenic effects when administered parenterally. Intravenous injections of sodium arsenate into hamsters on day 8 of gestation at dose levels of 15, 17.5, or 20 mg/kg/day resulted in exencephaly, encephaloceles, skeletal defects, and urogenital system abnormalities in fetuses (Ferm and Carpenter, 1968). Intraperitoneal injections of sodium arsenate, at doses levels of 30 mg/kg/day or higher, resulted in similar terata in rats and mice (Hood and Bishop, 1972; Beaudoin, 1974; Burk and Beaudoin, 1977).

3.4. TARGET ORGAN/CRITICAL EFFECTS

3.4.1. Oral Exposures

3.4.1.1. Primary Target Organs

1. Skin: Hyperpigmentation and hyperkeratosis in humans.

2. Nervous System: Peripheral neuropathy and CNS effects in humans.

3. Cardiovascular System: Peripheral and cardiovascular disorders in humans.

3.4.1.2. Other Target Organs

1. Blood: Hematological changes (anemia, leukopenia).

2. Liver: Liver swelling in humans; cirrhosis and portal hypertension in animals.

3. G.I. System: Gastroenteritis in humans and monkeys at high doses.

4. Reproductive Effects: Increased male to female birth ratio in animals and possibly in humans.

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target Organs

1. Skin: Dermatitis and possibly hyperpigmentation and hyperkeratosis in humans.

2. Nervous System: Peripheral neuropathy and CNS effects in humans.

3. Cardiovascular System: Peripheral vascular disorders in humans.

3.4.2.2. Other Target Organs

1. Respiratory system: Rhinitis, laryngitis, tracheobronchitis, pulmonary insufficiency, and nasal septum perforation.

2. Blood: Hematological changes (anemia, leukopenia).

3. Developmental Effects: Increase in spontaneous abortions, reduction in birth weight observed in animals and humans.

4. CARCINOGENICITY

4.1. ORAL EXPOSURES

4.1.1. Human

Epidemiological studies have revealed a close association between arsenic concentrations in drinking water and increased incidences of skin cancers, including squamous cell carcinomas and multiple basal cell carcinomas (U.S. EPA, 1987). Tseng et al. (1968) reported skin cancer rates of 2.6, 10.1 and 21.4 per 1000 in Taiwanese populations whose drinking water contained 0.30, 0.30-0.59, and 0.6 ppm As, respectively. No cases of skin cancer were seen in a control population of 7500 whose drinking water contained 0.001-0.017 ppm As. Cebrian et al. (1983) reported a 3.6-fold increase in skin lesions thought to be associated with epidermoid or basal cell carcinomas, in residents of a Mexican town whose drinking water contained 0.4 ppm As.

Chronic oral exposure to arsenic has also been linked to various types of internal cancers, including those of the liver, bladder, and respiratory and gastrointestinal tracts (U.S. EPA, 1987; IARC, 1987; Sommers and McManus, 1953; Reymann et al., 1978; Dobson et al., 1965; Chen et al., 1985, 1986).

4.1.2. Animal

Of the many studies conducted on laboratory animals, only a few have been able to show a positive association between oral exposure to arsenic and increased tumor incidence. Knoth (1966/67) reported increased incidences of adenocarcinomas of the skin, lung, peritoneum, and lymph nodes in NMRI mice dosed with arsenic trioxide or Fowler's solution once per week for 5 months (estimated total dose 7 mg/animal). Katsnelson et al. (1986) reported that arsenic trioxide induced a low incidence of adenocarcinomas at the site of its implantation in the stomach of rats. In addition, Shirachi et al. (1983)

reported that sodium arsenite enhanced the incidence of renal tumors induced in rats by intraperitoneal injection of the carcinogen *N*-nitrosodiethylamine.

4.2. INHALATION EXPOSURES

4.2.1. Human

Occupational exposure studies of smelter and pesticide workers have shown a close association between exposure to arsenic and lung cancer mortality (IARC, 1987; U.S. EPA, 1991a). A dose- and duration-dependent increased frequency of respiratory tract cancers was found in copper smelter workers exposed to air-borne arsenic concentrations averaging up to 62 mg/m^3 (arithmetic mean) (Lee and Fraumeni, 1969; Lee-Feldstein, 1983, 1986, 1989). Standardized mortality ratios (SMR) as high as 981 and a maximum relative risk of 6 were reported (Lee-Feldstein, 1986, 1989). At another smelter, lung cancer mortality rates were correlated with cumulative arsenic exposure as measured by urinary arsenic excretion values, and arsenic concentrations of 10 mg/m^3 were linked to a SMR greater than 200 (Enterline and Marsh, 1982; Enterline et al., 1987). Similarly, in a study of Swedish smelter workers, a clear positive dose-response relationship was found between cumulative arsenic exposure and lung cancer mortality and the overall SMR was 372 (Järup et al., 1989). Both proportionate mortality and cohort studies of pesticide workers have also shown an increased incidence of lung cancer deaths (Ott et al., 1974; Mabuchi et al., 1979).

An increased risk of lung cancer may also occur in non-occupationally exposed populations living in areas with high atmospheric levels of arsenic resulting from industrial emissions. Higher lung cancer rates have been reported in residents living near smelters (Brown et al., 1984; Pershagen 1985) and near an arsenic pesticide manufacturing plant (Matanoski et al., 1981).

4.2.2. Animal

Several animal studies have shown an association between tumor induction and exposure to arsenic by inhalation or intratracheal instillation. Ivankovic et al. (1979) reported that lung tumors developed in 9 of 15 BD IX rats given a single intratracheal instillation of Bordeaux mixture (4% calcium arsenate containing 0.07 mg As). In another study, calcium arsenate induced a borderline increase in lung adenomas following intratracheal instillation, but arsenic trisulfide had no effect on tumor incidence. Perinatal treatment of mice with arsenic trioxide resulted in the induction of lung adenomas (Rudnay and Börzsönyi 1981), and intratracheal instillation of the same compound in hamsters resulted in respiratory tract carcinomas, adenomas, papillomas and adenomatoid lesions (Ishinishi et al., 1983; Pershagen et al., 1984a,b).

4.3. OTHER ROUTES OF EXPOSURE

Osswald and Goerttle (1971) reported a high incidence (11/19) of lymphocytic leukemia or lymphomas in female Swiss mice injected intravenously with 0.5 mg As/kg (as sodium arsenate) once per week for 20 weeks. In a second study with pregnant mice injected subcutaneously with 0.5 mg/kg, once per day for 20 days during pregnancy, 11 of 24 developed the same types of tumors.

DiPaolo and Casto (1979) reported that sodium arsenate induced cell transformations *in vitro* in Syrian hamster embryo cells, and Casto et al. (1979) reported that sodium arsenite enhanced virus-induced cell transformation.

4.4. EPA WEIGHT-OF-EVIDENCE

4.4.1. Oral

Classification -- A; human carcinogen (U.S. EPA, 1991b)
Basis -- Increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations.

4.4.2. Inhalation

Classification – A; human carcinogen (U.S. EPA, 1991a)
Basis – Increased lung cancer mortality in populations exposed primarily through inhalation.

4.5. SLOPE FACTORS

4.5.1. Oral

SLOPE FACTOR: 1.0E-3 $(\mu g/kg/day)^{-1}$ (females) and 2.0E-3 $(\mu g/kg/day)^{-1}$ (males) (U.S. EPA, 1987). These slope factors were based on unit risks of 3E-5 (females) and 7E-5 $(\mu g/L)^{-1}$ (males) that were used to derive a single drinking water unit risk as shown below.

DRINKING WATER UNIT RISK: 5E-5 $(\mu g/L)^{-1}$ (U.S. EPA, 1991a).

PRINCIPAL STUDIES: Tseng et al., 1968; Tseng, 1977

VERIFICATION DATE: Not given.

COMMENT: The final unit risk is the arithmetic mean of the unit risks derived for females and males in a population in Taiwan exposed to arsenic in drinking water. Uncertainties associated with this unit risk involve the dose-response relationship, particularly in regard to (1) differential mortality due to other arsenic-induced diseases, (2) the possibility that ingestion of arsenic-contaminated foods contributed to the effects, and (3) the shape of the dose-response curve at low doses. A memorandum from the EPA administrator noted that the "uncertainties associated with ingested inorganic arsenic are such that estimates could be modified downwards as much as an order of magnitude, relative to risk estimates associated with most other carcinogens."

4.5.2. Inhalation

SLOPE FACTOR: 5.0E+1 $(mg/kg/day)^{-1}$ (U.S. EPA, 1992)

INHALATION UNIT RISK: 4.3E-3 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1991a)

PRINCIPAL STUDIES: Brown and Chu, 1983a-c, Lee-Feldstein, 1983; Higgins, 1982; Enterline and Marsh, 1982.

VERIFICATION DATE: 01/13/88

COMMENT: The final unit risk is the geometric mean of the geometric means for distinct exposed populations of workers at two different copper smelters. It was assumed that the increase in age-specific mortality was a function only of cumulative exposure. The unit risk should not be used if the air concentration exceeds 2 $\mu g/m^3$ (U.S. EPA, 1992).

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TOXICITY SUMMARY FOR CADMIUM

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EXECUTIVE SUMMARY

Cadmium is a naturally occurring metal that is used in various chemical forms in metallurgical and other industrial processes, and in the production of pigments. Environmental exposure can occur via the diet and drinking water (ATSDR, 1989).

Cadmium is absorbed more efficiently by the lungs (30 to 60%) than by the gastrointestinal tract, the latter being a saturable process (Nordberg et al., 1985). Cadmium is transported in the blood and widely distributed in the body but accumulates primarily in the liver and kidneys (Goyer, 1991). Cadmium burden (especially in the kidneys and liver) tends to increase in a linear fashion up to about 50 or 60 years of age after which the body burden remains somewhat constant. Metabolic transformations of cadmium are limited to its binding to protein and nonprotein sulfhydryl groups, and various macromolecules, such as metallothionein, which is especially important in the kidneys and liver (ATSDR, 1989). Cadmium is excreted primarily in the urine.

Acute oral exposure to 20-30 g have caused fatalities in humans. Exposure to lower amounts may cause gastrointestinal irritation, vomiting, abdominal pain, and diarrhea (ATSDR, 1989). An asymptomatic period of one-half to one hour may precede the onset of clinical signs. Oral LD_{50} values in animals range from 63 to 1125 mg/kg, depending on the cadmium compound (USAF, 1990). Longer term exposure to cadmium primarily affects the kidneys, resulting in tubular proteinosis although other conditions such as "itai-itai" disease may involve the skeletal system. Cadmium involvement in hypertension is not fully understood (Goyer, 1991).

Inhalation exposure to cadmium and cadmium compounds may result in effects including headache, chest pains, muscular weakness, pulmonary edema, and death (USAF, 1990). The 1-minute and 10-minute lethal concentration of cadmium for humans has been estimated to be about 2,500 and 250 mg/m^3, respectively (Barrett et al., 1947; Beton et al., 1966). An 8-hour TWA (time-weighted-average) exposure level of 5 mg/m^3 has been estimated for lethal effects of inhalation exposure to cadmium, and exposure to 1 mg/m^3 is considered to be immediately dangerous to human health (Friberg, 1950). Renal toxicity (tubular proteinosis) may also result from inhalation exposure to cadmium (Goyer, 1991).

Chronic oral RfDs of 5E-4 and 1E-3 mg/kg/day have been established for cadmium exposure via drinking water and food, respectively (U.S. EPA, 1991). Both values reflect incorporation of an uncertainty factor of 10. The RfDs are based on an extensive data base regarding toxicokinetics and toxicity in both human and animals, the critical effect being renal tubular proteinuria. Confidence in the RfD and data base is high.

Inhalation RfC values are currently not available.

The target organ for cadmium toxicity via oral exposure is the kidney (Goyer, 1991). For inhalation exposure, both the lungs and kidneys are target organs for cadmium-induced toxicity (ATSDR, 1989; Goyer, 1991).

There is limited evidence from epidemiologic studies for cadmium-related respiratory tract cancer (ATSDR, 1989). An inhalation unit risk of 1.8E-3 $(\mu g/m^3)^{-1}$ and an inhalation slope factor of 6.1E+0 $(mg/kg/day)^{-1}$ are based on respiratory tract cancer associated with occupational exposure (U.S. EPA, 1985). Based on limited evidence from multiple occupational exposure studies and adequate animal data, cadmium is placed in weight-of-evidence group B1 - probable human carcinogen.

1. INTRODUCTION

Cadmium (Cd) is a naturally occurring metallic element that is used for electroplating and galvanization processes, in the production of pigments, in batteries, as a chemical reagent, and in miscellaneous industrial processes (ATSDR, 1989). Cadmium compounds have varying degrees of solubility ranging from very soluble to nearly insoluble. The solubility affects their absorption and toxicity. Exposure to cadmium and cadmium compounds may occur in both occupational and environmental settings, the latter primarily via the diet and drinking water (ATSDR, 1989).

2. METABOLISM AND DISTRIBUTION

2.1. ABSORPTION

Cadmium is more efficiently absorbed from the lungs than from the gastrointestinal tract (ATSDR, 1989). The absorption efficiency is a function of solubility of the specific cadmium compound as well as its exposure concentration and route.

Inhalation absorption usually involves cadmium in a particulate matter form with absorption being a function of deposition, which in turn is dependent upon the particle size (particles 10 m diameter tend to be deposited in the upper airways and particles 0.1 m diameter are deposited in the alveolar region). Alveolar deposition efficiency in animal models ranges from 5 to 20% (Barrett et al., 1947; Boisset et al., 1978). Based on physiological modeling, cadmium deposition in the alveolar region of humans was estimated to be up to 50% for small particles (Nordberg et al., 1985). Actual cadmium absorption via inhalation exposure has been estimated to be 30 to 60% in humans (Friberg et al., 1974; Elinder et al., 1976).

Absorption of cadmium from the gastrointestinal tract appears to be a saturable process with the fraction absorbed decreasing at high doses (Nordberg et al., 1985). It is also important to distinguish true absorption from simple retention of cadmium in the microvilli of the small intestine (Foulkes et al., 1986). Shaikh and Smith (1980) reported a mean retention of 2.8% (1.1 to 7.0% range) for 12 human subjects given a single oral dose of radiolabeled cadmium chloride, and McLellan et al. (1978) reported 5.9% retention of cadmium chloride by 14 human subjects.

Also of importance relative to cadmium absorption is that its absorption may be decreased by divalent and trivalent cations (Zn^{+2}, Mg^{+2}, Cr^{+3}), and increased by iron and calcium deficiencies (Flanagan et al., 1978; Foulkes et al., 1986; Goyer, 1991). Dermal absorption is relatively unimportant (ATSDR, 1989).

2.2. DISTRIBUTION

Cadmium is transported in the blood by red blood cells and high-molecular-weight proteins such as albumin (Goyer, 1991). Normal blood cadmium levels in adults are < 1 g/dL. Although cadmium is widely distributed throughout the body, most (50 to 70% of the body burden) accumulates in the kidneys and liver (Goyer, 1991). Cadmium burden, especially in the kidneys, tends to increase in a linear fashion with age up to about 50 or 60 years of age after which the kidney levels remain somewhat constant or slightly decline (Goyer, 1991). There is evidence that the placenta is a partial barrier to cadmium, and that the fetus is exposed to only small amounts of maternal cadmium (ATSDR, 1989).

2.3. METABOLISM

As with most metallic elements, there is little or no direct metabolic conversions of cadmium, but rather binding to various biological components, such as protein and nonprotein sulfhydryl groups and anionic groups of various macromolecules (ATSDR, 1989). Of special importance, is the binding protein, metallothionein which is very effective in binding cadmium and some other metals and is instrumental in determining the disposition of cadmium in the body (e.g. concentration of cadmium in the kidneys).

2.4. EXCRETION

The principal route of excretion is via the urine, with average daily excretion for humans being about 2 to 3 g (ATSDR, 1989). Daily excretion represents only a small percentage of the total body burden, which accounts for the 17 to >30 years half-life of cadmium in the body (Tsuchiya et al., 1972; Friberg et al., 1974). Unabsorbed cadmium is removed from the gastrointestinal tract by fecal excretion. Typical daily cadmium excretion has been reported to be about 0.01% of the total body burden (ATSDR, 1989). There is some evidence for biliary excretion of cadmium (Klaassen et al., 1978).

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Doses of 1,500 to 8,900 mg (20 to 30 mg/kg) of cadmium have resulted in human fatalities, but generally, fatal poisoning from cadmium is rare (ATSDR, 1989). High doses of cadmium are known to cause gastrointestinal irritation resulting in vomiting, abdominal pain, and diarrhea (ATSDR, 1989). Lauwerys (1979) reported that the emetic threshold for cadmium in drinking water was about 15 mg/L and CEC (1978) reported that 3 mg was an emetic threshold.

Following ingestion of cadmium, an asymptomatic period of 0.5 to 1.0 hour may precede the onset of clinical signs. Depending on the severity of exposure, clinical signs of cadmium poisoning following acute exposure include: nausea, vomiting, abdominal cramps, headache, muscle cramps, exhaustion, shock, and death (USAF, 1990).

3.1.1.2. Animal

Oral LD_{50} values for animals range from 225 to 890 mg/kg for elemental cadmium, 63 to 88 mg/kg for cadmium chloride, 72 mg/kg for cadmium oxide, and 590 to 1125 mg/kg for cadmium stearate (USAF, 1990).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

Because the toxic effects of cadmium are a function of a critical concentration being attained in a target organ, similar effects will occur following long-term exposure to low cadmium levels and short-term exposure to high concentrations (Wang and Foulkes, 1984). Consequently, renal and hepatic toxicity may occur if toxic cadmium levels are attained in these organs even during subchronic exposure. A description of cadmium-induced toxicity following oral exposure is presented in Section 3.1.3. Generally, cadmium is not as toxic via oral routes as via inhalation.

3.1.2.2. Animal

Exposure of rabbits to 1.5 mmol cadmium chloride in drinking water (equivalent to 13 g/kg/day) produced histological alterations in the liver but no clinical signs of toxicity (Stowe et al., 1972). In a study by Kotsonis and Klaassen (1978), rats exhibited proteinuria after receiving cadmium chloride in the drinking water for six weeks at 30 or 100 mg/L (equivalent to 3.1 and 8.0 mg Cd/kg/day).

Although the effects of cadmium on the immune system of humans is unclear, evidence for cadmium-induced immunotoxicity in animals is available. Koller et al. (1975) noted a decrease in the number of spleen placque-forming cells in mice receiving cadmium at 0.6 mg/kg/day for 10 weeks, and Blakley (1985) reported a dose-dependent suppression of the humoral immune system in mice receiving cadmium in drinking water at concentrations of 5 to 50 mg/L for three weeks. These immune system effects occurred at kidney tissue concentrations (0.3 to 6.0 g/g) lower than those associated with renal toxicity.

3.1.3. Chronic Toxicity

3.1.3.1. Humans

The most serious chronic effect of oral exposure to cadmium is renal toxicity. This critical effect is characterized by tubular proteinuria resulting from renal tubular dysfunction. Friberg et al. (1974) estimated that this critical effect will not occur in humans until the cadmium concentration in the renal cortex exceeds 200 g/g.

Dietary intake of cadmium has also been implicated in osteomalacia, osteoporosis and spontaneous fractures, conditions collectively termed "itai-itai" (ouch-ouch) disease and originally documented in postmenopausal women in cadmium-contaminated areas of Japan (Friberg et al., 1974).

Cadmium exposure has also been implicated in hypertensive disorders, a situation that is currently not thoroughly understood or verified (ATSDR, 1989).

3.1.3.1. Animals

Rats given cadmium chloride in the drinking water at a concentration of 10 mg/L (1.2 mg Cd/kg/day) exhibited no renal effects even after 24 months, although higher exposure levels induced proteinuria after six weeks exposure (Kotsonis and Klaassen, 1978).

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

Developmental and reproductive toxicity in humans have not been demonstrated for oral exposure to cadmium (ATSDR, 1989).

3.1.4.1. Animal

Developmental toxicity data for cadmium administered orally to rats are equivocal. Pond and Walker (1975) reported few, if any effects, for rats exposed to cadmium chloride in the drinking water (15 mg/kg/day) during gestation. Baranski et al. (1985) reported teratogenic effects (fused or absent legs) in rats following gavage administration of cadmium chloride (40 mg/kg/day) during gestation. Neurological effects in rat pups were detected following gestational exposure to 0.4 or 4 mg Cd/kg (Baranski et al., 1986).

3.1.5. Reference Dose

3.1.5.1. Subchronic

ORAL RfD:	Not available
UNCERTAINTY FACTOR:	Not available
NOAEL:	Not available

3.1.5.2. Chronic

ORAL RfD:	5E-4 mg/kg/day (water) (U.S. EPA, 1991) 1E-3 mg/kg/day (food)
UNCERTAINTY FACTOR:	10 (for both food and water)
MODIFYING FACTOR:	1 (for both food and water)
NOAEL:	0.005 mg/kg/day (water) 0.01 mg/kg/day (food)
LOAEL:	Not available
CONFIDENCE:	
Study	Not applicable
Data base	High

RfD High

VERIFICATION DATE: 05/25/88

PRINCIPAL STUDY: The data supporting the RfD have been derived from many animal and human studies that have provided information on cadmium toxicity (renal toxicity using proteinuria as the critical effect) and the calculation of pharmacokinetic parameters regarding calcium absorption, distribution and excretion.

COMMENTS: Due to background cadmium in the diet, no subchronic RfD was calculated.

3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

3.2.1.1. Human

Inhalation of cadmium fumes or dust may result in a wide range of effects, including a metallic taste, headache, dyspnea, chest pains, cough with foamy or bloody sputum, and muscular weakness. Severe exposure may result in pulmonary edema and death (USAF, 1990). If the pulmonary edema is resolved, late-occurring kidney and/or liver damage may develop. Peculiar to inhalation exposure to cadmium is an asymptomatic period that may precede clinical illness by four to eight hours (USAF, 1990).

Based on cadmium lung burdens measured during postmortem examinations, Barrett et al. (1947) estimated a 1-minute lethal concentration of 2,500 mg/m^3. Beton et al. (1966) conducted similar calculations and reported a 10-minute lethal concentration of 250 mg/m^3. This value was further extrapolated to an 8-hour lethal concentration of 5 mg/m^3. Friberg et al. (1974) indicated that exposure to 1 mg Cd/m^3 for 8 hours is "immediately dangerous to humans" and the World Health Organization (WHO, 1980) identified 0.5 mg Cd/m^3 as the threshold for respiratory effects resulting from an 8-hour exposure.

3.2.1.2. Animal

Acute toxicity values (10-min. LC_{50}) for inhalation exposure of animals (monkeys, rats, mice, guinea pigs, dogs) to cadmium oxide range from 340 mg/m^3 to 15 g/m^3 (USAF, 1990).

3.2.2. Subchronic Toxicity

3.2.2.1. Human

Both pulmonary effects (emphysema, bronchiolitis, alveolitis) and renal effects (proteinuria) may occur following subchronic inhalation exposure to cadmium and cadmium compounds (ATSDR, 1989).

3.2.2.2. Animal

Pulmonary and renal toxicity have been documented for short-term inhalation exposure of animals to cadmium and cadmium compounds (USAF, 1990). Dose-dependent fibrotic lesions were observed in rats exposed to cadmium chloride aerosol at 0.3 to 1.0 mg/m^3, 6 hours/day for 12 weeks, but at a concentration of 2.0 mg/m^3 most rats died within 45 days (Kutzman et al., 1986). Friberg (1950) reported emphysema in rabbits exposed to cadmium chloride at 5 mg/m^3, 3 hours/day, 20 days/month for 8 months.

3.2.3. Chronic Toxicity

3.2.3.1. Human

Several occupational exposure studies have indicated that inhalation to cadmium dust and cadmium compounds may result in renal and pulmonary effects.

Bonnell (1955) reported that occupational exposure to cadmium oxide (1 to 270 g/m^3) resulted in proteinuria in 16% of the workers exposed for five years or more, and an increased incidence of emphysema in those exposed for more than 10 years. The latter group, however, may have received much higher initial exposures. Kidney lesions were also reported for the majority of workers exposed to the compound at a concentration of 20 g/m^3 for 27 years (Materne et al., 1975) and tubular proteinuria detected in workers exposed to cadmium dust (0.05 mg/m^3) for 6 to 12 years (Kjellstrom et al. 1977).

Based on occupational exposure studies, an 8-hour TWA (time-weighted-average) concentration of 0.02 mg/m^3 was established for a 20-year exposure to cadmium (OSHA, 1989), which is equivalent to continuous exposure to 0.007 mg/m^3 over a lifetime (ATSDR, 1989).

3.2.3.2. Animal

Chronic inhalation exposure studies for animals have demonstrated the carcinogenic potential of cadmium chloride and are discussed in Section 4.2.2.

3.2.4. Developmental and Reproductive Toxicity

3.2.4.1. Humans

Definitive data were not available regarding the developmental or reproductive toxicity of cadmium or cadmium compounds in humans.

3.2.4.2. Animal

Decreased fetal weight (with and without decreased maternal body weight) and minor neurobehavioral alterations in pups have been reported for rats exposed to cadmium oxide (0.16 mg/m^3) or cadmium sulfate (about 3 mg/m^3) during gestation (ATSDR, 1989). No other significant effects have been documented

3.2.5. Reference Concentration

The RfC for cadmium is currently under review (U.S. EPA, 1991).

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

No data were available regarding the acute toxicity of cadmium by other routes of exposure.

3.3.2. Subchronic Toxicity

No data were available regarding the subchronic toxicity of cadmium by other routes of exposure.

3.3.3. Chronic Toxicity

No data were available regarding the chronic toxicity of cadmium by other routes of exposure.

3.3.4. Developmental Toxicity

No data were available regarding the developmental toxicity of cadmium by other routes of exposure.

3.4. TARGET ORGANS/CRITICAL EFFECTS

3.4.1. Oral Exposures

3.4.1.1. Primary Target(s)

1. Kidney: Renal tubular proteinuria is the primary toxic effect of long-term cadmium exposure.

2. Gastrointestinal tract: Acute exposure to high levels of cadmium and cadmium compounds may cause irritation, vomiting, nausea, and diarrhea.

3.4.1.2. Other Target(s)

The liver, bones, testes, and cardiovascular system have been shown to be affected to various degrees by cadmium.

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target(s)

1. Kidney: Renal tubular proteinuria may result from chronic exposure to cadmium and cadmium compounds.

2. Lung: Inhalation exposure to cadmium dust, fumes, aerosols, and some cadmium compounds causes irritation of the respiratory tract, emphysema, and death for acute exposure to high cadmium concentrations.

3.4.2.2. Other Target(s)

No data were available indicating additional target organs/tissues for inhalation exposure to cadmium and cadmium compounds.

4. CARCINOGENICITY

4.1. ORAL EXPOSURE

4.1.1. Human

Limited epidemiologic studies have indicated that exposure to cadmium in food or drinking water is not carcinogenic (Bernard and Lauwerys, 1986).

4.1.2. Animal

Chronic exposure studies using animals exposed to cadmium in the diet or drinking water, have all provided negative results (ATSDR, 1989).

4.2. INHALATION EXPOSURE

4.2.1. Human

Limited evidence is available from epidemiologic studies indicating that inhalation exposure to cadmium may be associated with an increased incidence of respiratory tract cancer (ATSDR, 1989). An exposure-related increase in mortality due to lung cancer in workers with cumulative exposures of 585 to >2,920 mg Cd/m^3 (equivalent to TWA daily exposures of 168 to 2,522 g/ Cd/m^3) was reported by Thun et al. (1985).

Limited evidence is available showing that inhalation exposure to cadmium dust and fumes may be associated with prostate cancer, but the total number of cases in the various studies is small (ATSDR, 1989).

A unit risk of 1.8 10^{-3} ($g/m^3)^{-1}$ based on an increase in respiratory tract tumors in cadmium smelter workers was calculated by the U.S. EPA (1985).

4.2.2. Animal

Chronic exposure of rats to cadmium chloride aerosols (12.5, 25, or 50 g/m^3) produced a dose-related increase in the frequency of primary lung carcinomas (Takenaka et al., 1983).

4.3. OTHER ROUTES OF EXPOSURE

No data were available regarding the carcinogenic potential of cadmium by other routes of exposure.

4.4. EPA WEIGHT-OF-EVIDENCE CLASSIFICATION

4.4.1. Oral

Not assigned.

4.4.2. Inhalation

Classification-B1: Probable human carcinogen

Basis - Limited evidence from multiple occupational exposure studies showing an association between cadmium exposure and increased incidence of lung cancer. Adequate data are available showing a carcinogenic response to cadmium by rats and mice following inhalation exposure and parenteral administration.

4.5. CARCINOGENICITY SLOPE FACTORS

4.5.1. Oral

Not assigned.

4.5.2. Inhalation

SLOPE FACTOR:	6.1 $(mg/kg/day)^{-1}$
VERIFICATION DATE:	11/12/86
(U.S. EPA, 1985; 1991)	

COMMENT: The inhalation unit risk is based on occupational exposure of humans to cadmium fumes (Thun et al., 1985).

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TOXICITY SUMMARY FOR CHROMIUM

September 1992

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EXECUTIVE SUMMARY

Elemental chromium (Cr) does not occur in nature, but is present in ores, primarily chromite ($FeOCr_2O_3$) (Hamilton and Wetterhahn, 1988). Only two of the several oxidation states of chromium, Cr(III) and Cr(VI), are reviewed in this report based on their predominance and stability in the ambient environment and their toxicity in humans and animals.

Chromium plays a role in glucose and cholesterol metabolism and is thus an essential element to man and animals (Schroeder et al., 1962). Non-occupational exposure to the metal occurs via the ingestion of chromium-containing food and water, whereas occupational exposure occurs via inhalation (Langard, 1982; Pedersen, 1982). Workers in the chromate industry have been exposed to estimated chromium levels of 10-50 g/m^3 for Cr(III) and 5-1000 g/m^3 for Cr(VI); however, improvements in the newer chrome-plating plants have reduced the Cr(VI) concentrations 10- to 40-fold (Stern, 1982).

Chromium(III) is poorly absorbed, regardless of the route of exposure, whereas chromium(VI) is more readily absorbed (Hamilton and Wetterhahn, 1988). Humans and animals localize chromium in the lung, liver, kidney, spleen, adrenals, plasma, bone marrow, and red blood cells (RBC) (Langard, 1982; ATSDR, 1989; Bragt and van Dura, 1983; Hamilton and Wetterhahn, 1988). There is no evidence that chromium is biotransformed, but Cr(VI) does undergo enzymatic reduction, resulting in the formation of reactive intermediates and Cr(III) (Hamilton and Wetterhahn, 1988). The main routes for the excretion of chromium are via the kidneys/urine and the bile/feces (Guthrie, 1982; Langard, 1982).

Animal studies show that Cr(VI) is generally more toxic than Cr(III), but neither oxidation state is very toxic by the oral route. In long-term studies, rats were not adversely affected by ~1.9 g/kg/day of chromic oxide [Cr(III)] (diet), 2.4 mg/kg/day of Cr(III) as chromic chloride (drinking water), or 2.4 mg/kg/day of Cr(VI) as potassium dichromate (drinking water) (Ivankovic and Preussmann, 1975; MacKenzie et al., 1958).

The respiratory and dermal toxicity of chromium are well-documented. Workers exposed to chromium have developed nasal irritation (at <0.01 mg/m^3, acute exposure), nasal ulcers, perforation of the nasal septum (at ~2 g/m^3, subchronic or chronic exposure) (Hamilton and Wetterhahn, 1988; ATSDR, 1989; Lindberg and Hedenstierna, 1983) and hypersensitivity reactions and "chrome holes" of the skin (Pedersen, 1982; Burrows, 1983; U.S Air Force, 1990). Among the general population, contact dermatitis has been associated with the use of bleaches and detergents (Love, 1983).

Compounds of both Cr(VI) and Cr(III) have induced developmental effects in experimental animals that include neural tube defects, malformations, and fetal deaths (Iijima et al., 1983; Danielsson et al., 1982; Matsumoto et al., 1976).

The subchronic and chronic oral RfD value is 1 mg/kg/day for Cr(III). The subchronic and chronic oral RfD for Cr (VI) are 0.02 and 0.005 mg/kg/day, respectively (U.S. EPA, 1991a,b; 1992). The subchronic and chronic oral RfD values for Cr(VI) and Cr(III) are derived from no-observed-adverse-effect levels (NOAELs) of 1.47 g/kg Cr(III)/day and 25 ppm of potassium dichromate (Cr[VI]) in drinking water, respectively (Ivankovic and Preussmann, 1975; MacKenzie et al., 1958). The inhalation RfC values for both Cr(III) and Cr(VI) are currently under review by an EPA workgroup.

The inhalation of chromium compounds has been associated with the development of cancer in workers in the chromate industry. The relative risk for developing lung cancer has been calculated to be as much as 30 times that of controls (Hayes, 1982; Leonard and Lauwerys, 1980; Langard, 1983). There is also evidence for an increased risk of developing nasal, pharyngeal, and gastrointestinal carcinomas (Hamilton and Wetterhahn, 1988). Quantitative epidemiological data were obtained by Mancuso and Hueper (1951), who observed an increase in deaths (18.2%; $p<0.01$) from respiratory cancer among chromate workers compared with 1.2% deaths among controls. In a follow-up study, conducted when more than 50% of the cohort had died, the observed incidence for lung cancer deaths had increased to approximately 60% (Mancuso, 1975). The workers were exposed to 1-8 mg/m^3/year total chromium. Mancuso (1975) observed a dose response for total chromium exposure and attributed the lung cancer deaths to exposure to insoluble [Cr(III)], soluble [Cr(VI)], and total chromium. The results of inhalation studies in animals have been equivocal or negative (Nettesheim et al., 1971; Glaser et al, 1986; Baetjer et al., 1959; Steffee and Baetjer, 1965).

Based on sufficient evidence for humans and animals, Cr(VI) has been placed in the EPA weight-of-evidence classification A, human carcinogen (U.S. EPA, 1991a). For inhalation exposure, the unit risk value is 1.2E-2 ($g/m^3)^{-1}$ and the slope factor is 4.1E+01 $(mg/kg/day)^{-1}$ (U.S. EPA, 1991a).

1. INTRODUCTION

Elemental chromium (Cr) (CAS No. 7440-47-3) has an atomic weight of 51.996, a density of 7.2 g/mL at 28 C, a melting point of 1857 ± 20 C, a vapor pressure of 1 mm Hg at 1610 C, and is insoluble in water (Weast et al., 1988-1989). Elemental chromium does not occur in nature, but is present in ores, primarily chromite ($FeOCr_2O_3$) (Hamilton and Wetterhahn, 1988). Chromium can exist in several oxidation states, but only two of them, Cr(III) and Cr(VI), are considered in this report because of their predominance and stability in the ambient environment and their toxicological characteristics. Cr(III) results from the weathering of minerals and is the most stable state of environmental chromium. Cr(VI) in the environment is man-made, the result of contamination by industrial emissions (WHO, 1984; Hertel, 1986), and is the more toxic (U.S. EPA, 1984b). Examples of Cr(III) compounds include chromium acetate, chromium chloride, chromic oxide, and chromium sulfate; examples of Cr(VI) compounds include ammonium chromate, calcium chromate, potassium chromate, potassium dichromate, and sodium chromate (U.S. Air Force, 1990).

Chromium plays a role in glucose and cholesterol metabolism and is thus essential to man and animals (Schroeder et al., 1962). Reference values for chromium vary, but one source estimates a level of 70 ng/dL for whole blood [this includes Cr(VI) bound to red blood cells] and 14 ng/dL for serum (Tietz, 1986). The major non-occupational source of chromium for animals and humans is food, such as vegetables, meat, unrefined sugar, fish, vegetable oil, and fruits (Hertel, 1986; U.S. Air Force, 1990; U.S. EPA, 1984b). Other potential non-occupational sources include urban air, hip or knee prostheses, and cigarettes (U.S. EPA, 1984b).

Workers are exposed to chromium during its use in (1) the production of dichromate, (2) the chemical, stainless-steel, refractory and chromium-plating industries, and (3) the production and use of alloys (Langard and Norseth, 1986). Workers in the chromate industry encounter both Cr(III) and Cr(VI) (U.S. EPA, 1984). Chromium (III) concentrations in tanning facilities have been estimated at 10-50 g/m^3; the average concentration of Cr(VI) in fumes and dust of the various industries ranged from 5 to 1000 g/m^3 (Stern, 1982). Ten- to forty-fold reductions in Cr(VI) concentrations have been reported in modern chrome plating plants (Stern, 1982).

Chromium enters the body through the lungs, gastrointestinal tract and, to a lesser extent, the skin (Hamilton and Wetterhahn, 1988). Inhalation is the most important route for occupational exposure (Hertel, 1986). Although overt signs of chromium toxicity (e.g. perforation of the nasal septum, skin ulcers, and liver and kidney damage) are rarely seen today, some workers are still exposed to toxic concentrations of the metal (Hamilton and Wetterhahn, 1988). Non-occupational exposure occurs via the ingestion of chromium-containing food and water (Langard, 1982; Pedersen, 1982).

In the environment, Cr(III) is generally immobile in soil and is not very toxic to plants and animals (Kabata-Pendias and Pendias, 1984), whereas Cr(VI) is both mobile and toxic. Chromium (VI) in solution exists as hydrochromate ($HCrO_4$), chromate (CrO_4^{2-}), and dichromate ($Cr_2O_7^{2-}$) ionic species (U.S. EPA, 1984a) and reacts over time to form Cr(III) (U.S. EPA, 1984b).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

Chromium(III) and chromium(VI) exhibit different absorption characteristics. Chromium(III) is poorly absorbed, regardless of route of exposure, whereas chromium(VI) is more readily absorbed (Hamilton and Wetterhahn, 1988). In one study, for example, animals absorbed approximately 10% of an orally administered dose of Cr(VI), but less than 0.5% of the orally administered Cr(III) (Langard, 1982); therefore, the reduction of Cr(VI) to Cr(III) (which can occur in the stomach) may result in decreased absorption. In another study, humans and rats absorbed approximately 2% of the chromium that was administered orally as $Na_2{}^{51}CrO_4$ and measured in the urine (humans) and feces (rat) as ^{51}Cr (Donaldson and Barreras 1966). However, when $Na_2{}^{51}CrO_4$ was administered intraduodenally and intrajejunally, absorption of the administered dose was ~50% in humans and ~25% in animals.

The detection of chromium in the urine, serum, and red blood cells (RBC) of humans exposed in the workplace suggests that the metal is absorbed following inhalation exposure. Limited experimental data indicate that water-soluble inhaled Cr(VI) is absorbed rapidly (Langard et al., 1978). Rats exposed to 7.35 mg/m^3 of zinc chromate dust for 1, 100, 250 and 350 minutes had chromium levels in the blood of 0.007, 0.024, 0.22, and 0.31 g/mL, respectively. Animals were also exposed to the same concentration of zinc chromate 6 hours/day for 4 days and blood levels were measured at the end of each day. Blood chromium levels peaked at the end of the second exposure and began to decline at the end of the third exposure.

Both Cr(VI) and Cr(III) compounds can be absorbed by the skin, but the degree of absorption is apparently determined by valence state, anionic form and concentration and pH of the solution (U.S. EPA, 1984c).

2.2. DISTRIBUTION

Humans and animals exhibit similar patterns of distribution for chromium. Workers exposed to chromium by inhalation had levels of the metal in the lung, liver, kidney, and adrenals that were 300-fold, 2- to 4-fold, 10-fold, and 10- to 50-fold higher, respectively, than those in of controls (Langard, 1982). Workers also exhibit elevated chromium levels in the urine, serum [Cr(III) and Cr(VI)] and RBC [Cr(VI) only] (ATSDR, 1989). Animals exposed by intratracheal or intravenous injection distributed both Cr(III) and Cr(VI) throughout the body, but mainly to the lungs, spleen, bone marrow, liver, and kidney (Bragt and van Dura, 1983; Hamilton and Wetterhahn, 1988).

Chromium (given in drinking water to rats for one year as potassium chromate or chromic chloride and to dogs for 4 years as potassium chromate) was distributed to the bone (rat only), liver, kidney, and spleen (MacKenzie et al. 1958; Anwar et al., 1961). Other studies have demonstrated higher tissue levels in animals receiving Cr(VI) in the drinking water than those receiving Cr(III) (ATSDR, 1989).

2.3. METABOLISM

Chromium is not biotransformed, but Cr(VI) undergoes enzymatic reduction, resulting in the formation of reactive intermediates and Cr(III) (Hamilton and Wetterhahn, 1988). *In vitro* and under physiologic conditions, ascorbic acid, the thiols, glutathione, cysteine, cysteamine, lipoic acid, coenzyme A, and coenzyme M reduce Cr(VI) at a significant rate (Hamilton and Wetterhahn, 1988). The *in vitro* reaction of Cr(VI) with glutathione results in the formation of a Cr(V) intermediate that is possibly the form that interacts with cellular macromolecules (Jennette, 1982). DT-diaphorase is a major cytosolic enzyme involved in Cr(VI) reduction (DeFlora et al., 1985). The NADPH-dependent Cr(VI) reductase activity of rat liver microsomes has been attributed to cytochrome P-450, whereas the Cr(VI) reductase activity of rat liver mitochondria is attributed to NADH-ubiquinone oxidoreductase (complex I) (Hamilton and Wetterhahn, 1988).

2.4. EXCRETION

The main routes for the excretion of chromium are via the kidneys/urine and the bile/feces; minor routes include milk, sweat, hair, and nails (Guthrie, 1982; Langard, 1982). Studies in humans and/or animals have shown that chromium administered orally or intravenously is excreted principally in the urine, whereas

chromium administered by inhalation or intratracheal injection is excreted in both the urine and the feces (Love 1983; Hamilton and Wetterhahn, 1988).

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

For humans, the estimated lowest lethal dose is 71 mg/kg for chromium (oxidation state not identified) (Sax and Lewis, 1989) and 1-5 g for unspecified Cr(VI) compounds (Leonard and Lauwerys, 1980; Langard and Norseth, 1986).

3.1.1.2. Animal

Oral LD_{50} values for Cr(VI) compounds range from 54 mg/kg for ammonium dichromate in the rat (Gad et al., 1986) to 300 mg/kg for potassium chromate in the mouse (Shindo et al., 1989). Oral LD_{50} values for Cr(III) and Cr(II) compounds in the rat are 11.26 g/kg (chromic acetate) and 1.87 mg/kg (chromous chloride), respectively (Smyth et al., 1969). Animals given lethal doses of sodium chromates, potassium dichromate, or ammonium dichromate exhibited hypoactivity, lacrimation, mydriasis, diarrhea, changes in body weight, pulmonary congestion, fluid in the stomach and intestine, and erosion and discoloration of the gastrointestinal mucosa (Gad et al., 1986). Lethal doses of chromium trioxide produce cyanosis, tail necrosis, diarrhea, and gastric ulcers (Kobayashi, 1976). Because the gastrointestinal absorption of chromium is poor, the oral toxicity of the metal has been attributed to other than systemic poisoning, e.g. gastrointestinal bleeding (Hamilton and Wetterhahn, 1988).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

Information on the subchronic toxicity of chromium following oral exposure in humans was unavailable.

3.1.2.2. Animal

In one study, BD rats received 2 or 5% chromic oxide [Cr(III)] in the diet for 90 days (total doses, 72-75 g/kg or 160-170 g/kg) (Ivankovic and Preussmann, 1975). Food consumption and body weight were monitored and serum protein, bilirubin, hematology, urinalysis, organ weights, and histopathology were evaluated. Other than 12-37% reductions in the absolute weights of the livers and spleens at the higher dose, no adverse effects were observed.

In another study, MacKenzie et al. (1958) administered 0-25 ppm of Cr(III) (as chromic chloride) or Cr(VI) (as potassium dichromate) in drinking water to groups of male and female rats for one year, and saw no effect on body weight, gross external condition, histopathology, and blood chemistry at any dose. Microscopic examination revealed accumulations of chromium in the liver, kidneys, bone, and spleen (MacKenzie et al., 1958). The No Adverse Effect Level (NOAEL) of 25 ppm was used to calculate the chronic and subchronic oral RfD values for Cr(VI) (U.S. EPA, 1991a).

3.1.3. Chronic Toxicity

3.1.3.1. Human

Information on the chronic toxicity of chromium following oral exposure in humans was unavailable.

3.1.3.2. Animal

Animals appear to tolerate long-term oral treatment with chromium. Ivankovic and Preussmann (1975) conducted a feeding study in which male and female rats were fed chromic oxide [Cr(III)] baked in bread at levels of 0, 1, 2, or 5%, 5 days/week for 600 feedings (over 840 days). The total doses given were 360, 720, and 1800 g/kg body weight. After termination of exposure, animals that died or were killed when moribund were examined for microscopic lesions. The investigators did not mention other specific toxicologic parameters, but did report that adverse effects were not observed in any of the groups. The U.S. EPA (1991b) selected the 5% level as the no-observed-effect level (NOEL) to be used in the derivation of a chronic oral RfD.

Dogs (2/group) were not adversely affected by exposure to 0, 0.45, 2.25, 4.5, 6.75, and 11.2 ppm potassium chromate in the drinking water for 4 years (Anwar et al., 1961). The toxicologic evaluation consisted of gross and microscopic analysis of all major organs, urinalysis, and weights of spleen, liver and kidney. Assuming an average water consumption for the dog of 0.0275 L/kg/day, the U.S. EPA (1984a) converted the highest dose tested, 11.2 ppm, to the NOEL of 0.31 mg potassium chromate/kg/day [0.089 mg Cr(VI)/kg/day].

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

Information on the developmental or reproductive toxicity of chromium following oral exposure in humans was unavailable.

3.1.4.2. Animal

As part of a 90-day feeding study, male and female BD rats received 2% or 5% chromium oxide 5 days/week (Ivankovic and Preussmann, 1975). During the last 30 days of treatment, males and females from each treatment group were paired for a developmental toxicity assay. All females became pregnant, the gestation period was normal, and the young had no malformations or other adverse effects. One group of progeny, observed for 600 days, developed no tumors. The investigators concluded that no toxic or teratogenic effects resulted from treatment of both males and females with chromium oxide prior to and throughout the gestation period. No other information on the developmental or reproductive toxicity of chromium following oral exposure in animals was available.

3.1.5. Reference Dose

3.1.5.1. Subchronic

3.1.5.1.1. Chromium(III)

ORAL RfD:	1.0 mg/kg/day (as an insoluble salt) (U.S. EPA, 1991b)
UNCERTAINTY FACTOR:	100
NOAEL:	5% Cr_2O_3 in diet 5 days/week for 90 days (1468 mg/kg Cr(III)/day)

COMMENT: The principal study (Ivankovic and Preussmann, 1975) is the same for the subchronic and chronic RfD and is described in section 3.1.3.2.

3.1.5.1.2. Chromium(VI)

ORAL RfD:	0.02 mg/kg/day (U.S. EPA, 1991b)
UNCERTAINTY FACTOR:	100
NOAEL:	25 ppm (mg/L) of chromium as K_2CrO_4 converted to 2.4 mg of Cr(VI)/kg/day.

COMMENT: The principal study (MacKenzie et al., 1958) is the same for the subchronic and chronic RfD and is described in section 3.1.2.2.

3.1.5.2. Chronic

3.1.5.2.1. Chromium(III)

ORAL RfD:	1.0 mg/kg/day (as an insoluble salt) (U.S. EPA, 1991c)
UNCERTAINTY FACTOR:	1000
NOEL:	5% Cr_2O_3 in diet 5 days/week for 600 feedings (1800 g/kg b.w. average total dose; 1468 mg/kg Cr(III)/day)

CONFIDENCE:

Study	Low
Data Base	Low
RfD	Low

VERIFICATION DATE: 11/21/85

PRINCIPAL STUDY: Ivankovic and Preussmann, 1975

COMMENTS: The NOEL was based on no effects reported at the highest dose tested in a one year feeding study in rats. The RfD is limited to metallic Cr(III) of soluble salts (U.S. EPA, 1991c). The uncertainty factor of 1000 reflects a factor of 10 to account for interspecies variability, a factor of 10 for interhuman variability in the toxicity of the chemical in lieu of specific data, and an additional modifying factor of 10 for uncertainty in the NOEL.

3.1.5.2.2. Chromium(VI)

ORAL RfD: 0.005 mg/kg/day (U.S. EPA, 1991a)
UNCERTAINTY FACTOR: 500
NOAEL: 25 mg/L of chromium as K_2CrO_4 for one year, converted to 2.4 mg of Cr(VI)/kg/day.

CONFIDENCE:
Study Low
Data Base Low
RfD Low

VERIFICATION DATE: 02/05/86

PRINCIPAL STUDY: MacKenzie et al., 1958

COMMENTS: The NOAEL was based on no effects reported at the highest dose tested in a one year drinking water study in rats. The RfD is limited to metallic Cr(VI) of soluble salts (U.S. EPA, 1991). The calculation assumed drinking water consumption of 0.097 L/kg/day. The uncertainty factor of 500 reflects a factor of 10 to account for interspecies variability and a factor of 10 for interhuman variability in the toxicity of the chemical in lieu of specific data, and an additional factor of 5 to compensate for the less-than-lifetime exposure duration of the study (U.S. EPA, 1991a).

3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

3.2.1.1. Human

Estimated LC_{50} values for humans range from 5 mg/m^3 for zinc chromate [Cr(VI)] (Sax and Lewis, 1989) to 94 mg/m^3 for potassium dichromate [Cr(VI)] (Gad et al., 1986). The inhalation of chromium can cause nasal ulcers and perforation of the nasal septum (Hamilton and Wetterhahn, 1988). The perforation lesions do not disappear when exposure ceases. Nasal irritation has been observed following short-term exposure to chromium levels of <0.01 mg/m^3 (ATSDR, 1989).

3.2.1.2. Animal

The estimated LC_{50} values (mg/m^3) in the Sprague Dawley rat (males and females combined) exposed to Cr(VI) compounds are: 158 for ammonium dichromate, 104 for sodium chromate, 124 for sodium dichromate, and 94 for potassium dichromate (Gad et al., 1986). Clinical signs of toxicity include respiratory distress and irritation and body weight loss (Gad et al., 1986). Lethality data were not found for Cr(III) compounds.

3.2.2. Subchronic Toxicity

3.2.2.1. Human

The respiratory tract is the target of subchronic inhalation exposure to chromium compounds. In one study, chromeplaters exposed to hot chromic acid concentrations <1.4 mg/m^3 for less than one year exhibited various symptoms including simple scarring and perforation of the nasal septum, dental lesions, coughing and expectoration, sneezing, and nasal irritation (Gomes, 1972).

3.2.2.2. Animal

Johansson et al. (1986a, 1986b) exposed rabbits to aerosols of sodium chromate [0.9 mg of Cr(VI)/m^3] or chromium nitrate [0.6 mg of Cr(III)/m^3], 6 hours/day, 5 days/week for 4-6 weeks and examined the lungs and pulmonary macrophages for adverse effects. Neither compound affected lung morphology, but macrophages in both groups were enlarged, multinucleated, or vacuolated, and accumulated

in intraalveolar or intrabronchiolar spaces as nodules ("naked" granulomas). In addition to producing morphological changes, the chromium nitrate also reduced the phagocytic activity of the cells.

Immunological effects have been noted following subchronic exposure to chromium compounds. In rats, 0.2 mg/m^3 Cr(VI) (90-days continuous exposure) depressed the activity of alveolar macrophages and the humoral immune response, whereas 0.1 mg/m^3 Cr(VI) stimulated phagocytic activity of the alveolar macrophages and increased the humoral immune response (Glaser et al., 1985).

Nettesheim et al. (1971) reported rapid weight loss, fatty liver, distended and atrophic intestines, and early death in C57Bl/6 mice exposed to calcium chromate concentrations of 30 mg/m^3. The study was preliminary and exposure duration was described only as "subchronic".

3.2.3. Chronic Toxicity

3.2.3.1. Human

Long-term exposure to chromium produced various effects in workers in the chromium industry. For example, nine chromeplaters exposed to chromic acid concentrations of 0.18 to 1.4 mg/m^3 for 0.5-12 months, had upper respiratory tract lesions that ranged from nasal itching and soreness to septal ulcerations and perforations (Kleinfeld and Rosso, 1965). Thirty-five of thirty-seven chromeplaters, engaged in using the hot chromic acid process for 0.3 months to 11 years and exposed to air concentrations of 7.1 g total Cr/m^3 and 2.9 g Cr(VI)/m^3, developed nasal lesions that ranged from shallow erosions to frank perforations (Cohen et al., 1974). Forty-three Swedish chrome-plating workers, exposed to chromic acid [Cr(VI)] for a median of 2.5 years, were examined for respiratory symptoms (Lindberg and Hedenstierna, 1983). A dose-response was observed for nasal symptoms. Workers exposed to concentrations of <1-2 g/m^3 (8-hour mean) complained of runny nose and stuffy nose ($p<0.05$); workers exposed to >2 g/m^3 suffered ulceration and perforation of the nasal mucosa.

3.2.3.2. Animal

Nettesheim et al. (1971) exposed C57Bl/6 mice to calcium chromate dust concentrations of 13 mg/m^3 [4.33 mg Cr(VI)/m^3, as calculated by U.S. EPA (1984)] 5 hours/day, 5 days/week for the lifetime of the animals. Sizes of 99% of the calcium chromate particles averaged 1.0 micron. Toxicity in the animals, as evidenced by decreased body weight gain, was observed after 6 months of exposure. Other non-carcinogenic effects observed in animals exposed for 6 months or longer included marked hyperplasia, necrosis, and atrophy of the bronchial epithelium; bronchiolization of alveoli (growth of the bronchial epithelium into alveoli); proteinosis of terminal bronchioli and alveoli (emphysema-like changes); extreme dilation of alveolar ducts and disruption of alveolar membranes; atrophy of spleen and liver; and enlargement, followed by atrophy of the lymph nodes (particularly tracheal and submandibular).

In other studies: (1) rats and rabbits exposed to 3 to 4 mg/m^3 of potassium dichromate [Cr(VI)] and sodium chromate [Cr(VI)] 4 hours/day, 5 days/week for life developed nasal perforations and foreign-body type inflammation of the lung, but did not develop systemic effects (Stefee and Baetjer, 1965); (2) Wistar rats, exposed continuously to 100 g Cr/m^3 [Cr(III) and Cr(VI)] as chromium oxide for 18 months, exhibited a slight increase in white blood cells, and significant increases in red blood cell, hemoglobin and hematocrit values (Glaser et al., 1986); and (3) rats and hamsters exposed to calcium chromate aerosol levels of 2 mg/m^3 (0.67 mg Cr(VI)/m^3) for 589 days over a period of 891 days had laryngeal hyperplasias and metaplasias (Laskin et al., 1972). Non-specific effects of inhalation exposure to Cr(III) and Cr(VI) included pneumonia in mice and "nuisance dust reaction" in rats (Baetjer et al., 1959; Lee et al. 1988).

3.2.4. Developmental and Reproductive Toxicity

Information on the developmental or reproductive toxicity of chromium following inhalation exposure in humans and animals was unavailable.

3.2.5. Reference Concentration

The inhalation RfC values for both Cr(III) and Cr(VI) are currently under review by an EPA workgroup.

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

3.3.1.1. Human

Dermal exposure to chromium compounds can induce contact dermatitis or the formation of lesions that, without treatment, can develop into deep ulcers or "chrome holes". The chrome holes usually heal when exposure ceases (Pedersen, 1982; Burrows, 1983).

3.3.1.2. Animal

LD_{50} values (mg/kg) for chromium compounds applied to the skin of New Zealand rabbits (male and female combined) are 1.64 for ammonium dichromate, 1.6 for sodium chromate, 1.00 for sodium dichromate, and 1.7 for potassium dichromate (Gad et al., 1986). Lethal doses of these chemicals produced dermal necrosis, corrosion, edema and erythema; eschar formation; diarrhea; and hypoactivity. Non-lethal doses of the dichromates were also tested for corrosion and irritation potential. Based on a four-hour exposure time and a 48-hour observation period, the chemicals, in the dry solid form, were not corrosive, but sodium dichromate and ammonium dichromate caused erythema in some animals. When moistened with saline, the chemicals were not corrosive but all were irritating.

Dermal hypersensitivity reactions are elicited by both Cr(III) and Cr(VI) compounds (U.S. Air Force, 1990). For example, Schwarz-Speck and Grundmann (1972) induced hypersensitivity in the guinea pig with chromium sulfate ([Cr(III)] dissolved in Triton X-100 and with potassium dichromate [Cr(VI)] in an aqueous solution and in the BALB/c and ICR mice with potassium dichromate in dimethyl sulfoxide (Mor et al., 1988). BALB/c mice treated with potassium dichromate in Triton X-100 or methanol did not develop hypersensitivity (Mor et al., 1988).

For injected trivalent and hexavalent chromium compounds, the kidney is the main target for toxicity (U.S. EPA, 1984b). Gumbleton and Nicholls (1988) examined the effect of single subcutaneous doses of potassium dichromate on the release of tissue enzymes into the urine, an early and sensitive indicator of renal toxicity. The enzyme assays were conducted 52-727 hours after injection. There was no effect on the enzymes at 6 mg/kg. At doses of 10, 15, and 20 mg/kg, excretion rates for the cytosolic and lysosomal enzymes (aspartate aminotransferase and lactate dehydrogenase) and the lysosomal enzyme (*N*-acetyl-ß-D-glucosamidase) were increased while brush border enzymes (γ-glutamyl transferase, alkaline phosphatase, and leucine aminopeptidase) were unchanged. The enzyme changes were accompanied by dose-related necrosis of the proximal tubules in the outer cortex of the kidney and loss of alkaline phosphatase from the outer cortex of the kidney. Necrosis of the inner cortex of the kidney and loss of alkaline phosphatase from that tissue were observed at the highest dose. The effects appeared to be transient.

3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of chromium by other routes of exposure in humans and animals was unavailable.

3.3.3. Chronic Toxicity

Information on the chronic toxicity of chromium by other routes of exposure in humans and animals was unavailable.

3.3.4. Developmental and Reproductive Toxicity

3.3.4.1. Human

Information on the developmental or reproductive toxicity of chromium by other routes of exposure in humans was unavailable.

3.3.4.2. Animal

Danielsson et al. (1982) reported that radioactive sodium dichromate [Cr(VI)], injected into pregnant mice was more efficiently taken up by the fetus than radioactive chromic chloride [Cr(III)]. Nevertheless, compounds of both Cr(VI) and Cr(III) have induced developmental effects in experimental animals. In one study, for example, one noninbred and two inbred strains of hamsters injected intravenously with 5 mg/kg of chromium trioxide [Cr(VI)] on day 8 of gestation and sacrificed on day 15 exhibited cleft palate and external malformations that included edema, omphalocele, tail bud abnormalities and encephalocele. The noninbred strain also had increased resorptions and hydrocephalus.

In another study, Matsumoto et al. (1976) administered 19.5 mg Cr/kg as chromic chloride [Cr(III)] to pregnant mice by subcutaneous injection on days 7, 8, or 9 of gestation and examined the fetuses on day 18. The highest frequency of fetal deaths occurred with the day 9 injection and the highest number of malformations (exencephaly, open eyelids, cleft palate, and fused ribs) occurred with the day 8 injection. Further studies (injection on day 8 of gestation) demonstrated a dose response for the effects. No significant fetal effects were noted with 9.76 mg Cr/kg administered as chromic chloride every other day from day 0 to day 16 of gestation.

Iijima et al. (1983) administered 19.5 mg Cr/kg as chromic chloride [Cr(III)] to pregnant mice by intraperitoneal injection on day 8 of gestation and observed pyknosis within the neuroepithelium and defects in the neural tube 8 and 24 hours, respectively, after injection.

3.4. TARGET ORGANS/CRITICAL EFFECTS

3.4.1. Oral Exposures

3.4.1.1. Primary Target Organs

The poor gastrointestinal absorption of chromium and its low oral toxicity preclude the identification of primary target organs/critical effects.

3.4.1.2. Secondary Target Organs

Gastrointestinal system: Animals exposed to very high doses acute of chromium exhibit diarrhea, gastric ulcers, and discoloration and erosion of the gastric mucosa, most likely local, rather than systemic effects.

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target Organs

The primary target organ for the subchronic/chronic toxicity of chromium is the respiratory system as evidenced by various symptoms in humans that range from irritation of the respiratory tract to perforation of the nasal septum and symptoms in animals that include severe bronchiolar and alveolar damage.

3.4.2.2. Other Target Organs

1.Immune system: In rats, accumulations of alveolar macrophages formed "naked granulomas" in the bronchioles and alveoli of rabbits. In rats the activity of alveolar macrophages and the humoral immune response were depressed, whereas phagocytic activity of the alveolar macrophages and the humoral immune response were increased.

2. Spleen and liver: Mice exhibited atrophy of the spleen and liver.

3.4.3. Other Routes of Exposure

3.4.3.1. Primary Target Organs

1. Skin: Acute dermal toxicity is characterized by dermatitis and the formation of "chrome holes" in humans and by dermatitis and dermal hypersensitivity in animals.

2. Fetus: Compounds of both Cr(III) and Cr(VI), injected into pregnant animals, induced fetal toxicity and fetal malformations.

3.4.3.2. Other Target Organs

Kidney: Injection of Cr(VI) caused renal enzyme changes and necrosis.

4. CARCINOGENICITY

4.1. ORAL EXPOSURES

4.1.1. Human

Information on the carcinogenicity of chromium by oral exposure in humans was unavailable.

4.1.2. Animal

Chromium was not carcinogenic in Sprague-Dawley rats exposed to 25 ppm of potassium chromate [Cr(VI)] and chromic chloride [Cr(III)] in their drinking water for one year (MacKenzie et al., 1958), or in male or female BD rats exposed to 5% chromic oxide [Cr(III)] in food 5 days/week for over 2 years (total dose, 1800 g/kg body weight) (Ivankovic and Preussmann, 1975).

4.2. INHALATION EXPOSURES

4.2.1. Human

Workers occupationally exposed to chromium are considered to be at risk for developing lung cancer (Hayes, 1982; Leonard and Lauwerys, 1980; Langard, 1983; Mackison et al. 1981; Mancuso and Hueper, 1951; Mancuso, 1975; Sano and Mitohara, 1978). The relative risk for developing lung cancer has been calculated to be up to 30 times that of controls (Hayes, 1982; Leonard and Lauwerys, 1980; Langard, 1983). There is also evidence for an increased risk of developing nasal, pharyngeal, and gastrointestinal carcinomas (Hamilton and Wetterhahn, 1988). Many of the early epidemiology studies failed to identify the specific etiologic agent [i.e. Cr(III) or Cr(VI)] (U.S. EPA, 1984b).

Mancuso and Hueper (1951) investigated lung cancer incidence in a cohort of workers employed for more than one year (from 1931-1949) in a chromate production plant. In the county where the plant was located, 34 of 2931 deaths (1.2%) of control males were due to respiratory cancer, whereas among the chromate workers, 6 of 33 deaths (18.2%; $p<0.01$) were due to respiratory cancer. Mancuso (1975) then followed 332 workers (employed from 1931-1951) until 1974, when more than 50% of the cohort had died. The workers were exposed to 1-8 mg/m^3/year total chromium. Incidences for cancer deaths were 63.6% for men employed from 1931-1932, 62.5% for men employed from 1933-1934, and 58.3% for those employed from 1935-1937. Mancuso (1975) observed a dose response for total chromium exposure and attributed the lung cancer deaths to exposure to insoluble [Cr(III)], soluble [Cr(VI)], and total chromium. However, the U.S. EPA (1984b) questioned the correlation because of small sample number.

Studies of workers in the chrome pigment industry revealed a correlation between exposure to Cr(VI) and lung cancer (Langard and Norseth, 1975; Davies, 1978, 1979; Frentzel-Beyme, 1983). Studies from the chrome-plating industry either showed a correlation (Royle, 1975; U.S. EPA, 1984a) or were inconclusive (Silverstein et al., 1981; Okubo and Tsuchiya, 1979; U.S. EPA, 1984a) regarding lung cancer and exposure to

chromium compounds. Studies of ferrochromium workers were also inconclusive regarding lung cancer risk (Pokrovskaya and Shabynina, 1973; Langard et al., 1980, 1990; Axelsson et al., 1980).

4.2.2. Animal

The results of inhalation studies in animals are equivocal regarding the carcinogenicity of chromium.

Nettesheim et al. (1971) observed an increase in the incidence of pulmonary adenomas and decreased tumor latency in C57Bl/6 mice exposed to 13 mg/m^3 calcium chromate dust [4.33 mg Cr(VI)/m^3, as calculated by U.S. EPA (1984)] 5 hours/day, 5 days/week for life. Ninety-nine percent of the calcium chromate particles were 1.0 micron. Early mortality among the unexposed controls may have affected cumulative tumor incidence, but examination of groups of animals dying of lung tumors at subsequent 10-week periods revealed that at 60-70 and 70-80 weeks (approximately 30 animals/group), none of the unexposed mice died with lung tumors, whereas 5 and >6%, respectively, of the exposed mice died with lung tumors (animal numbers not clear). The significance of the study was questioned because statistical analysis was not performed (U.S. EPA, 1984a). IARC (1980) concluded that the study did not show a significant increase in treatment-related tumors.

Glaser et al. (1986) observed "weak" tumor responses in groups of 20 rats exposed for 18 months to 100 g/m^3 sodium dichromate dust (3 lung tumors) or to the slightly soluble chromium oxide containing both Cr(VI) and Cr(III) in a ratio of 3:2 (1 lung tumor). Lee et al. (1988) described a unique tumor in the lungs of rats exposed to 0.54-22 mg/m^3 of chromium dioxide [Cr(IV)] 6 hours/day, 5 days/week for 2 years. The tumor (in 2/108 females, but not in males) was described as a cystic keratinizing squamous cell carcinoma. The investigators indicated that the tumors were devoid of characteristics of true malignancy and have negligible relevance to man.

In other studies, mice and rats exposed to mixed chromate dust (~1 mg/m^3) containing both Cr(III) and Cr(VI) did not develop tumors (Baetjer et al., 1959); and neither did rabbits, guinea pigs or rats exposed, 4-5 hours/day, 1 to 2 times/week for life, to various mixes of chromate dust either with or without chromate mist (Steffee and Baetjer, 1965).

4.3. OTHER ROUTES OF EXPOSURE

Chromium(VI) induces cancer in experimental animals at some sites of exposure, whereas chromium(III) does not. Chromium(VI) induced tumors (1) at the site of intrapleural implantation as calcium chromate (Hueper and Payne, 1962), (2) at the site of intrabronchial implantation as strontium, calcium, or zinc chromate (Levy and Martin, 1983), and (3) in the rat lung following intratracheal injection of sodium chromate and calcium chromate (Steinhoff et al., 1983). However, there is no evidence in humans and little evidence in animals that skin cancer is induced by topical application of chromium (Hayes, 1982; Leonard and Lauwerys, 1980; Langard, 1983).

4.4. EPA WEIGHT-OF-EVIDENCE

4.4.1. Chromium(III)

Chromium(III) has not been evaluated by the U.S. EPA for evidence of human carcinogenic potential (U.S. EPA, 1991b).

4.4.2. Chromium(VI)

4.4.2.1. Oral

Not assigned.

4.4.2.2. Inhalation

Classification -- A; human carcinogen

Basis – Sufficient evidence for humans and animals (U.S. EPA, 1991a). "Results of occupational epidemiologic studies of chromium-exposed workers are consistent across investigators and study populations. Dose response relationships have been established for chromium exposure and lung cancer. Chromium-exposed workers are exposed to both chromium III and chromium VI compounds. However, because only chromium VI has been found to be carcinogenic in animals studies, it was concluded that only chromium(VI) should be classified as a human carcinogen" (U.S. EPA, 1991a).

4.5. SLOPE FACTORS [Chromium(VI)]

4.5.1. Oral

Not available.

4.5.2. Inhalation

SLOPE FACTOR:	4.1E+01 $(mg/kg/day)^{-1}$
INHALATION UNIT RISK:	1.2E-2 ($g/m^3)^{-1}$
PRINCIPAL STUDY:	Mancuso, 1975
VERIFICATION DATE:	06/26/86
(U.S. EPA, 1991a)	

COMMENT: Extrapolation method, multistage, extra risk (U.S. EPA, 1991a). Based on dose response data for inhalation carcinogenicity in humans (Mancuso, 1975).

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MERCUR

TOXICITY SUMMARY FOR MERCURY

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EXECUTIVE SUMMARY

Mercury is a naturally occurring element existing in multiple forms and in various oxidation states. It is used in a wide variety of products and processes. In the environment, mercury may undergo transformations among its various forms and among its oxidation states. Exposure to mercury may occur in both occupational and environmental settings, the latter primarily involving dietary exposure (ATSDR, 1989).

Absorption, distribution, metabolism, and excretion of mercury is dependent upon its form and

oxidation state (ATSDR, 1989; Goyer, 1991). Organic mercurials are more readily absorbed than are inorganic forms. An oxidation-reduction cycle is involved in the metabolism of mercury and mercury compounds by both animals and humans (ATSDR, 1989). The urine and feces are primary excretory routes. The elimination half-life is 35 to 90 days for elemental mercury and mercury vapor, and about 40 days for inorganic salts (Goyer, 1991).

Ingestion of mercury metal is usually without effect (Goldwater, 1972). Ingestion of inorganic salts may cause severe gastrointestinal irritation, renal failure and death with acute lethal doses in humans ranging from 1-4 g (ATSDR, 1989). Mercuric (divalent) salts are usually more toxic than are mercurous (monovalent) salts (Goyer, 1991). Mercury is also known to induce hypersensitivity reactions such as contact dermatitis and acrodynia (pink disease) (Mathesson et al., 1980). Inhalation of mercury vapor may cause irritation of the respiratory tract, renal disorders, CNS effects characterized by neurobehavioral changes, peripheral nervous system toxicity, renal toxicity (immunologic glomerular disease), and death (ATSDR, 1989).

Toxicity resulting from subchronic and chronic exposure to mercury and mercury compounds usually involves the kidneys and/or nervous system, the specific target and effect being dependent on the form of mercury (ATSDR, 1989). Organic mercury, especially methyl mercury, rapidly enters the central nervous system (CNS) resulting in behavioral and neuromotor disorders (ATSDR, 1989; Goyer, 1991). The developing CNS is especially sensitive to this effect, as documented by the epidemiologic studies in Japan and Iraq where ingestion of methyl mercury-contaminated food resulted in severe toxicity and death in adults and severe CNS effects in infants (Bakir et al., 1973; Amin-Zaki et al., 1974; Harada et al., 1978). Blood mercury levels of <10 g/dL and 300 g/dL corresponded to mild effects and death, respectively (Bakir et al., 1973). Teratogenic effects due to organic or inorganic mercury exposure do not appear to be well documented for humans or animals, although some evidence exists for mercury-induced menstrual cycle disturbances and spontaneous abortions (Derobert and Tara, 1950; Amin-Zaki, 1974; ATSDR, 1989).

A subchronic and chronic oral RfD of 0.0003 mg/kg/day for methyl mercury is based on the ambient level required to produce a blood mercury level of 200 ng Hg/mL (U.S. EPA, 1991a,1992). A subchronic and chronic oral RfD of 0.0003 mg/kg/day for inorganic mercury has been proposed and is based on immunologic glomerulonephritis (U.S. EPA, 1992). A Lowest-Observed-Adverse-Effect-Level (LOAEL) of 0.317 mg Hg/kg/day for inorganic mercury was identified in the key study (Bernaudin et al., 1981). No-Observed-Adverse-Effect-Levels (NOAELs) were not available for oral exposure to inorganic mercury or methyl mercury. A subchronic and chronic inhalation RfC of 0.0003 mg Hg/m^3 for inorganic mercury has been proposed (U.S. EPA, 1992) and is based on neurological disorders (increased frequency of intention tremors) following long-term occupational exposure to mercury vapor (Fawer et al., 1983). The LOAELs for subchronic and chronic inhalation exposures to inorganic mercury are 0.32 and 0.03 mg Hg/m^3, respectively. NOAELs were unavailable. An inhalation RfC for methyl mercury has not been determined.

No data were available regarding the carcinogenicity of mercury in humans or animals. The U.S. EPA has placed inorganic mercury in weight-of-evidence classification D, not classifiable as to human carcinogenicity (U.S. EPA 1991b). Methyl mercury has not been evaluated by the U.S. EPA for evidence of human carcinogenic potential and no carcinogenicity slope factors have been calculated.

1. INTRODUCTION

Mercury (Hg) is a naturally occurring element that may exist in elemental, inorganic, or organic forms, and in various oxidation states. Mercury is used in a wide variety of products and processes, including pressure sensitive devices (thermometers, barometers), electrical apparatus (wiring, switches, batteries), paints, pharmaceuticals, and in the production of various chemicals (ATSDR, 1989). The oxidation state and chemical form of mercury are important in determining its toxicity, with mercurous salts (monovalent mercury) being less toxic than mercuric salts (divalent mercury). Organic mercurials such as methyl mercury are highly toxic. In the environment, mercury may undergo transformations among the various oxidation states and chemical forms. Both environmental and occupational exposure are relevant to mercury and its compounds, although environmental exposure is unimportant for mercury vapor. Mercury intake from occupational exposure is of greater significance than that from environmental exposure. Environmental exposure to mercury may involve dietary intake (especially from fish) and possibly from dental amalgams, the latter source being controversial (ATSDR, 1989; Langworth et al., 1991).

2. METABOLISM AND DISTRIBUTION

2.1. ABSORPTION

Generally, organic mercurials are absorbed much more rapidly than are inorganic forms. However, approximately 80% of mercury vapor is absorbed following inhalation exposure. Data on the inhalation absorption of organic mercury are limited and inconclusive. Metallic mercury and mercurous salts (e.g. Hg_2Cl_2) are poorly absorbed (<0.10%) following oral exposure (Friberg and Nordberg, 1973). Absorption of mercuric chloride by adult mice was reported to be only 1-2% (Clarkson, 1971) but 1-week old mice absorbed 38% of the orally administered compound. Gastrointestinal absorption of inorganic salts of mercury from food is <15% for mice and about 7% for humans (Goyer, 1991). Organic mercury compounds (methyl- and phenylmercury) have been shown to readily absorbed (>80%) by humans and animals following oral exposure (ATSDR, 1989; Goyer, 1991).

2.2. DISTRIBUTION

Being lipid soluble, mercury vapor readily enters the red blood cells and the CNS following inhalation exposure. The kidneys will exhibit the greatest concentration of mercury following exposure to inorganic mercury salts. Organic mercury is readily distributed throughout the body but tends to concentrate in the brain and kidneys (ATSDR, 1989; Goyer, 1991). Mercury is known to bind to microsomal and mitochondrial enzymes resulting in cell injury and death. Mercury in renal cells localizes in lysosomes (Madsen and Christensen, 1971). Petersson et al. (1991) administered ^{203}Hg-labeled methyl mercury intraperitoneally to rabbits twice weekly for nine weeks. After one week of treatment, the highest concentration of ^{203}Hg was detected in the fur with substantially lower levels being found in the kidney, liver, brain, muscle, and blood. Inorganic mercury levels in the liver of the rabbits increased with time after cessation of treatment. A report by Dutczak et al. (1991) providing data for guinea pigs, hamsters and a macaque monkey indicate that extensive absorption of methyl mercury occurs in the gall bladder. Subsequent biliary-hepatic cycling of the compound may contribute to the long biologic half-life of methyl mercury. Yoshida et al. (1991) reported that substantial concentrations of metallothionein-associated mercury were found in the kidneys and livers of neonate guinea pigs exposed to mercury vapor for 120 minutes on the day of birth. Metallothionein synthesis increased in the liver but not in the kidneys. Animal data indicate that all forms of mercury cross the placenta, and that mercury levels may be 2-fold greater than in maternal levels with fetal red blood cells containing mercury levels 30% higher than maternal red blood cells (Goyer, 1991).

2.3. METABOLISM

Mercury is not destroyed by metabolism but rather converted to different forms and oxidation states. The metabolism of mercury and mercury compounds appears to be similar for animals and humans (ATSDR, 1989), and involves an oxidation-reduction cycle. Inhaled mercury vapor is rapidly oxidized to the divalent form in red blood cells (Halbach and Clarkson, 1978). Oxidation of elemental mercury also occurs in the lungs of humans and animals (Magos et al., 1973; Hursh et al., 1980), and there is some evidence for hepatic-mediated oxidation (Magos et al., 1978). Animal studies have provided some data suggesting that the divalent inorganic mercury cation may be further reduced to elemental mercury (Clarkson and Rothstein, 1964; Dunn et al., 1981). Organic mercury compounds are also converted to divalent mercury by cleavage of the carbon-mercury bond (Goyer, 1991) with subsequent metabolism occurring via the oxidation

mercury bond (Goyer, 1991) with subsequent metabolism occurring via the oxidation reduction cycle. Aryl mercury compounds (e.g. phenylmercury) undergo this conversion more readily than do the short-chain (methyl) mercury compounds. No evidence of demethylation of methyl mercury by the brain of rabbits was noted following parenteral administration of the compound (Petersson et al., 1991).

2.4. EXCRETION

The urine and feces are the primary routes for the excretion of inorganic mercury by humans (ATSDR, 1989). Following brief exposure of humans to inorganic mercury, urinary excretion accounts for 13% of the total body burden, whereas this value increases to 58% for long-term exposure. For inorganic mercury, the urinary levels do not parallel blood levels (ATSDR, 1989). Henderson et al. (1974) identified three forms of mercury in the urine of occupationally-exposed individuals: elemental mercury, a reducible mercuric-cysteine complex, and a large complex in which the mercury can only be released following organic destruction. The data available for elemental mercury and mercury vapor indicate half-times for these forms to be 35 to 90 days (Goyer, 1991). The biologic half-time for inorganic mercury salts is about 40 days.

Fecal elimination is an important excretory route following exposure to organic mercury compounds (Norseth and Clarkson, 1970). However, Petersson et al. (1991) using ^{203}Hg-labeled methyl mercury administered intraperitoneally to rabbits twice weekly for nine weeks, showed that 12 weeks after cessation of treatment 54% of administered dose had been excreted in the urine and only 5% had been excreted in the feces.

The elimination of organic mercury compounds generally follows first-order kinetics with whole body clearance times and blood clearance times being longer than for inorganic mercury. The biologic half-time for methyl mercury is about 70 days. There is some evidence that females tend to excrete organic mercury faster than males (Aberg et al., 1969; Miettinen, 1973). Additional excretory routes include saliva, bile, and sweat (ATSDR, 1989).

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Generally, any form of mercury in high acute doses may cause tissue damage resulting from the ability of mercury to denature proteins, thereby disrupting cellular processes (WHO, 1976). However, oral exposure to mercury metal is usually without serious effects. A dose of 200 g caused no adverse health effects in a 2-year old child and unspecified large amounts were without effect in adults (Goldwater, 1972).

Ingestion of inorganic salts of mercury such as mercury bichloride (corrosive sublimate) may cause gastrointestinal disorders including pain, vomiting, diarrhea and hemorrhage, and renal failure resulting in death. Additional effects of acute mercury poisoning include shock and cardiovascular collapse (WHO, 1976). Acute lethal doses in humans range from 1 to 4 g (10-42 mg Hg/kg for a 70 kg adult) for inorganic mercuric salts (ATSDR, 1989)

A hypersensitivity reaction to mercurous compounds such as mercurous chloride (calomel) is characterized by vasodilation, hyperkeratosis, and hypersecretion of the sweat glands. Children exhibiting this condition, also known as acrodynia or pink disease, may also develop fever, a pink-colored rash, swelling of the spleen and lymph nodes, and hyperkeratosis and swelling of the fingers (Matheson et al., 1980; Goyer, 1991).

The effects of acute exposure to organic mercury compounds are not well documented. However, exposure to organomercurials are known to contribute to the body burden of mercury and have resulted in serious developmental and neurological effects as reported in the following sections.

3.1.1.2. Animal

The acute toxicity of inorganic mercury in animals is similar to that observed in humans (ATSDR, 1989). Neurological effects and death have been reported for various animal species receiving inorganic mercury orally (ATSDR, 1989). The LD_{50} values in animals for elemental mercury range from 10 to 40 mg/kg (WHO, 1976).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

The effects of subchronic exposure to mercury and mercury compounds are likely to be similar to those of chronic exposure if the exposure level and body burden of mercury is increased (see Section 3.1.3.1.). Renal toxicity and neurological effects would be the most typical effects associated with subchronic exposure.

In Iraq, over 6000 individuals were hospitalized and 459 individuals died as a result of consuming bread prepared with flour made from wheat and barley treated with a methylmercurial fungicide (Bakir et al., 1973). Methyl mercury concentration in the wheat flour ranged from 4.8-14.6 g/g (mean=9.1 g/g). The clinical symptoms included paresthesia, visual disorders, dysarthria, and deafness. The most severe cases resulted in coma and death due to CNS failure. Based on data obtained during this incident, a dose-response relationship between blood mercury levels (<10 g/dL to 500 g/dL), and frequency and severity of symptoms showed that mild symptoms occurred at the lower blood mercury levels and that deaths occurred at levels >300 g/dL.

3.1.2.2. Animal

Oral exposure to inorganic mercury has produced neurological, immunological and systemic effects in rodents exposed for periods of 1-11 weeks. The no-observed-adverse-effect level (NOAEL) for these

studies was 0.42 mg/kg/day, and the lowest-observed-adverse effect level (LOAEL) was 0.8 mg/kg/day (ATSDR, 1989).

In a 110-day exposure of mice to mercuric chloride (1 or 3 mg/kg/day) only decreased body weight gain was noted (Ganser and Kirschner, 1985).

Behavioral and pathological effects were reported for cats receiving methyl mercury at doses of 0.01 mg/kg/day for 11 months or 0.45 mg/kg/day for 83 days, and for rats receiving the compound at 0.6-2.4 mg/kg/day for 8 weeks or 1 mg/kg/day for 11 weeks (USAF, 1990). Systemic, neurological and developmental effects resulting from subchronic, oral exposure to organic mercury have been reported for various species of rodents (ATSDR, 1989). Necrosis and degeneration of brain tissue were reported for rabbits exposed to metallic mercury vapor (0.86 mg/m^3) for 12 weeks (Ashe et al., 1953).

3.1.3. Chronic Toxicity

3.1.3.1. Human

Chronic oral exposure to mercury or mercury compounds may affect the CNS, gastrointestinal tract and the kidneys; the renal effect, in part, involving an immunologically-mediated response (ATSDR, 1989). Davis et al. (1974) reported dementia, colitis, and renal failure in two women chronically (6 and 25 years) ingesting a mercurous chloride-containing laxative. Generally, little information is available regarding the toxicity of inorganic mercury following chronic oral exposure.

Exposure to organic mercury causes CNS effects, especially in the fetus and neonate. Although any exposure to organic mercury compounds will contribute to the body burden of mercury, exposure during pregnancy or the postnatal period has the most significant consequences as discussed in Section 3.1.4.

3.1.3.2. Animals

Chronic oral exposure (2 years) of rats to inorganic mercury produces glomerulonephritis (Fitzhugh et al., 1950).

Neurological as well as other systemic toxic effects have resulted following chronic oral exposure of animals to organic mercury compounds (ATSDR, 1989). Neurotoxic effects indicative of CNS involvement have been reported for mice and rats orally administered organic mercury compounds (usually methyl mercury) for several weeks to over a year (ATSDR, 1989). Glomerulonephrotic changes were observed in rats fed phenylmercuric acetate for two years (Fitzhugh et al., 1950). Monkeys orally exposed to methyl mercury for 1000 days at doses adjusted to maintain a blood mercury level of 100-400 g/mL, exhibited reduced sensitivity to visual stimulation, somesthetic impairment, and incoordination (Evans et al., 1977). Rice and Gilbert (1982) noted impaired spatial vision in monkeys given methyl mercury at 0.05 mg/kg/day from birth until 3-4 years of age.

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

No information was available regarding developmental/reproductive toxicity of inorganic mercury in humans following oral exposure.

The developmental toxicity of organic mercury is best exemplified by the epidemic poisonings by methyl mercury in Iraq and Minamata and Niigata, Japan. Although no evidence of teratogenicity was observed, Amin-Zaki et al. (1974) found other severe developmental effects (impaired motor and mental function, hearing loss and blindness) in infants of mothers exposed via contaminated grain during the Iraqi epidemic. The most severely affected infants had mercury blood levels ranging from 319 to 422 g Hg/dL. It is also important to note that a 45% mortality rate was reported for pregnant women with signs of mercury poisoning versus a 7% mortality rate for the general population. In Minamata and Niigata, Japan, methyl mercury poisoning resulted from the ingestion of fish that had accumulated methyl mercury and other mercury compounds resulting from contaminated surface waters (WHO, 1976). Harada (1978) reported that at about 6 months of age 13 of the 220 infants prenatally exposed to methyl mercury during the Minamata Bay incident

showed signs of mercury poisoning characterized by instability of the neck, convulsions, and severe neurological and mental impairment. Choi et al. (1978) reported abnormal cytoarchitecture of the brain in infants prenatally exposed to methyl mercury. No other significant anatomical defects have been reported.

3.1.4.2. Animal

Only limited information was available regarding the developmental toxicity of inorganic mercury. Gale (1974) reported an increase in fetal resorptions in hamsters receiving a single oral dose of mercuric chloride (31.4 mg Hg/kg). This study also identified a dose of 15.7 mg Hg/kg as a NOAEL for hamsters based on the absence of developmental toxicity.

A 100% incidence of neonatal deaths and failure of dams to deliver was reported for rats receiving dietary methylmercuric chloride equivalent to 5 mg Hg/kg/day (Khera and Tabacova, 1973). The investigators reported no maternal toxicity.

Ultrastructural changes in the nervous system of mice exposed in utero to methylmercuric hydroxide (up to 10 mg Hg/kg/day) were reported by Hughes and Annau (1976). A dose of 3 mg Hg/kg/day produced significant behavioral changes in the mice. Ultrastructural changes in the nervous system have also been reported for rats prenatally exposed to methylmercuric chloride (4 mg Hg/kg/day) (Chang et al., 1977).

Exposure of rats to methyl mercury in the drinking water (0.25-0.50 mg Hg/kg/day) from 1 month prior to mating to the end of gestation resulted in ultrastructural changes in the livers of the fetuses (Fowler and Woods, 1977).

In their study using monkeys exposed from birth to 3 or 4 years of age (Section 3.1.3.1.), Rice and Gilbert (1982) noted that the young, developing monkeys were especially vulnerable to the toxic effects of methyl mercury on visual function as demonstrated by the low dose at which these effects occurred.

Pregnant monkeys (Macaca fascicularis) given methyl mercury in apple juice (50 or 90 g methyl mercury/kg/day resulting in blood mercury levels of 1.0±0.13 ppm or 2.0±0.33 ppm, respectively) exhibited a decrease in pregnancy rate and increased abortion rate for mercury blood levels above 1 ppm (Mottet et al., 1985).

3.1.5. Reference Dose

3.1.5.1. Subchronic

Inorganic mercury:

ORAL RfD:		3E-4 mg/kg/day (U.S. EPA, 1992)
UNCERTAINTY FACTOR:	1000	
NOAEL:		Not available
LOAEL:		0.317 mg Hg/kg/day

PRINCIPAL STUDY: Bernaudin et al., 1981

Methyl mercury:

ORAL RfD:		3E-4 mg/kg/day (U.S. EPA, 1992)
UNCERTAINTY FACTOR:	10	
MODIFYING FACTOR:		1
NOAEL:		None
LOAEL:		200 ng Hg/mL blood equivalent to 0.003 mg Hg/kg/day
CONFIDENCE:		
Study:	Medium	
Data base:	Medium	
RfD:	Medium	

PRINCIPAL STUDY: Clarkson et al., 1976; Nordberg and Strangert, 1976; WHO, 1976

COMMENTS: The RfD is based on an exposure that would produce a blood level of 200 gn Hg/mL, which is the blood concentration associated with early mercury-induced health effects in humans.

3.1.5.2. Chronic

Inorganic mercury:

ORAL RfD:	3E-4 mg/kg/day (U.S. EPA, 1992)
UNCERTAINTY FACTOR:	1000
MODIFYING FACTOR:	None
NOAEL:	Not available
LOAEL:	0.317 mg Hg/kg/day
CONFIDENCE:	Not available (see comments)

VERIFICATION DATE: See comments

PRINCIPAL STUDY: Bernaudin et al., 1981

COMMENTS: RfD is not yet verified but the review panel is in concordance with the data (U.S. EPA, 1991).

Methyl mercury:

ORAL RfD:	3E-4 mg/kg/day (U.S. EPA, 1991a)
UNCERTAINTY FACTOR: 10	
MODIFYING FACTOR:	1
NOAEL:	None
LOAEL:	200 ng Hg/mL blood equivalent to 0.003 mg Hg/kg/day
CONFIDENCE:	
Study: Medium	
Data base: Medium	
RfD: Medium	

VERIFICATION DATE: 12/02/85 (U.S. EPA, 1991)

PRINCIPAL STUDY: Clarkson et al., 1976; Nordberg and Strangert, 1976, WHO, 1976

COMMENTS: RfD is based on an exposure that would produce a blood level of 200 ng Hg/mL, which is the blood concentration associated with early mercury-induced health effects in humans.

3.2. INHALATION EXPOSURES

3.2.1. Acute Toxicity

3.2.1.1. Human

Inhalation of mercury vapor may result in corrosive bronchitis, interstitial pneumonitis, and death (Goyer, 1991). Systemic effects following inhalation exposure may include shock, renal disorders, and CNS effects characterized by lethargy and neurobehavioral effects (insomnia, loss of memory, excitability, etc.). Occupational exposure to metallic mercury vapor at concentrations of 1.1 to 44 mg/m^3 for 4 to 8 hours produced chest pains, dyspnea, cough, hemoptysis, impairment of pulmonary function, and interstitial pneumonitis (ATSDR, 1989). Acute effects of inorganic mercury poisoning may be accompanied by a metallic taste, sore gums, and excessive salivation.

A case report cited an incident wherein four adults were acutely exposed to mercury vapor resulting from the smelting of dental amalgams (Taueg et al., 1991). Initial signs of toxicity included nausea, diarrhea, dyspnea, and chest pains. Despite chelation therapy, all four patients died 11 to 24 days after initial exposure. Mercury concentrations in the house were as high as 912 g/m^3 at or within 11 to 188 days after the exposure, and postmortem blood mercury levels ranged from 58 to 369 g/L.

Historically, the triad of increased excitability, tremors, and gingivitis has been recognized as characteristic for mercury poisoning (Goyer, 1991).

3.2.1.2. Animal

Death resulting from severe pulmonary edema has been reported for mice, guinea pigs, and rats following inhalation exposure to mercury vapor (Christensen et al., 1937). Similarly, inhalation exposure of rabbits to mercury vapor at a concentration of 1 to 1.1 mg/m^3 for 1 to 30 hours resulted in death (Ashe et al., 1953). This same study also showed that 30-hour exposure of rabbits to mercury vapor at a concentration of 28.8 mg/m^3 caused extensive necrosis of the lungs.

Data are lacking regarding the effects of inhalation exposure of animals to organic mercury compounds (ATSDR, 1989).

3.2.2. Subchronic Toxicity

3.2.2.1. Human

Subchronic inhalation exposure to mercury vapor will result in effects similar to those for acute exposure, and will vary depending on exposure severity and duration. Sax and Lewis (1989) reported a lowest toxic exposure level of 0.15 mg/m^3 for human females exposed to mercury vapor for 46 days. Sexton et al. (1976) reported tremors (especially in activities requiring fine control), insomnia, and nervousness resulting from 7 to 25 weeks of exposure to mercury vapor.

Langolf et al. (1978) noted that short-term exposure to high levels of mercury appears to induce greater neurological effects than does long-term exposure to lower mercury levels.

Exposure of humans to diethylmercury at vapor concentrations of 1 to 1.1 mg/m^3 for 4 to 5 months resulted in death, the cause of which was not determined (Hill, 1943). Data are lacking regarding inhalation exposure to methyl mercury.

3.2.2.2. Animal

The effects of subchronic inhalation exposure to mercury or mercury compounds is dependent on the exposure concentration and the specific form of mercury. Low levels of exposure will generally affect the kidney and CNS while high-level exposure will target the respiratory, cardiovascular, and gastrointestinal systems as described in Section 3.1. Exposure of rabbits to mercury vapor (0.86-6.0 mg/m^3) for 2 to 12 weeks resulted in marked degeneration and necrosis of the heart (Ashe et al., 1953). Subchronic inhalation exposure of rats and rabbits to mercury has also produced neurobehavioral changes (ATSDR, 1989). Evidence for a systemic autoimmune response was reported by Bernaudin et al. (1981) for rats inhaling vapors of mercuric chloride or methyl mercuric chloride 4 hours/day for 60 days. The kidney, lungs, and spleen were identified as target organs.

3.2.3. Chronic Toxicity

3.2.3.1. Human

Chronic exposure to low levels of mercury vapor may induce immunologic glomerular disease (Goyer, 1991). A number of studies have been conducted with individuals occupationally exposed to inorganic mercury compounds (mercuric oxides, mercurial chlorides, mercuric nitrate) and are reviewed in USAF (1990). Briefly, neuropsychological symptoms (insomnia, fatigue, headaches, etc.) and renal effects that correlated with blood mercury levels were reported for those exposed 2 years. The emotional and psychological disturbances often referred to as the "Mad Hatter Syndrome" has been attributed to inhalation of the dust or vapors of mercuric nitrate used in the making of felt hats (Clarkson, 1989).

Chronic exposure to mercury vapor results in CNS effects including fatigue and tremors, and gingivitis (Goyer, 1991). As exposure increases, the frequency and magnitude of muscle tremors increase and are accompanied by personality and behavioral changes (memory loss, excitability, depression, and hallucinations).

Chronic exposure to low levels of mercury may affect the peripheral nervous system resulting in polyneuropathies (reduced sensory and motor nerve function), and neuropsychological effects (visual

alterations, sensory loss, stress) (ATSDR, 1989), these effects correlating with tissue levels of 20-40 g/g. Fawer et al. (1983) reported an increase in the frequency of intention tremors of workers exposed to mercury vapor (time-weighted-average [TWA] of 0.026 mg/m^3) over an average of 26 years. Neuropsychological effects were also reported by Smith et al (1970) for occupational exposure to mercury levels of >0.1 mg/m^3. Mercury concentrations below this value did not appear to cause observable effects.

Inhalation exposure to alkyl mercury compounds may occur during the manufacture or use of alkylmercury fungicides. The effects reported for these compounds include paresthesia of the extremities, mouth and lips, constriction of the visual field, deafness, motor incoordination and compromised reflex function. In severe cases, loss of speech and mental deterioration may occur (McComish et al., 1988).

3.2.3.2. Animal

Chronic inhalation exposure (72-83 weeks) of rats, rabbits and dogs to metallic mercury vapor (0.01 mg/m^3) did not produce histological evidence of renal toxicity (Ashe et al., 1953). Additional information on the chronic inhalation toxicity of inorganic mercury in animals was not available.

Information regarding the toxicity of organic mercury following chronic exposure of animals was not available.

3.2.4. Developmental and Reproductive Toxicity

3.2.4.1. Humans

There is evidence that chronic exposure of women to metallic mercury vapor may increase the frequency of menstrual disturbances and spontaneous abortions (Derobert and Tara, 1950; ATSDR, 1989). Mishonova et al. (1980) reported an increased frequency of pregnancy complications for women occupationally exposed to metallic mercury vapor.

No data were available regarding the developmental/reproductive toxicity potential of inhaled organic mercury compounds.

3.2.4.2. Animal

Steffek et al. (1987) showed that exposure of pregnant rats to metallic mercury vapor at concentrations of 0.5 mg/m^3 on gestational days 10-15 caused an increase in resorptions and congenital defects in the offspring.

Prolongation of the estrus cycle of rats exposed to metallic mercury vapor at concentrations of 2.6 mg/m^3, 6 hours/day for 21 days was reported by Baranski and Szmczyk (1973). This same study also showed that gestational exposure of rats to metallic mercury vapor (2.5 mg/m^3) resulted in a decrease in the number of living fetuses and increased pup mortality.

3.2.5. Reference Concentration

3.2.5.1. Subchronic

Inorganic mercury:

INHALATION RfC:		0.0003 mg Hg/m^3 (U.S. EPA, 1992)
UNCERTAINTY FACTOR:	30	
MODIFYING FACTOR:		None
NOAEL:		0.009 mg Hg/m^3

PRINCIPAL STUDY: Fawer et al., 1983

Methyl mercury:

Not available.

3.2.5.2. Chronic

Inorganic mercury:

INHALATION RfC:		0.0003 mg Hg/m^3 (U.S. EPA, 1991b)
UNCERTAINTY FACTOR:	30	
MODIFYING FACTOR:		None
NOAEL:		0.009 mg Hg/m^3
CONFIDENCE:	Not available	

VERIFICATION DATE: Not verified (U.S. EPA, 1992)

PRINCIPAL STUDY: Fawer et al. (1983)

COMMENTS: RfC is not yet verified but the review panel is in concordance with the data.

Methyl mercury:

Not available.

3.3. OTHER ROUTES OF EXPOSURE

3.3.1. Acute Toxicity

Dermal contact with organic or inorganic mercury compounds may cause dermatitis especially in hypersensitive individuals (USAF, 1990). Renal effects have been reported following dermal exposure to organic mercurials, and neurological effects have been reported for dermal exposure to inorganic mercury (ATSDR, 1989).

No data are available for other routes of exposure.

3.3.2. Subchronic Toxicity

No information was available regarding the subchronic toxicity of mercury by other routes of exposure.

3.3.3. Chronic Toxicity

No information was available regarding the chronic toxicity of mercury by other routes of exposure.

3.3.4. Developmental Toxicity

No information was available regarding developmental toxicity of mercury by other routes of exposure.

3.4. TARGET ORGANS/CRITICAL EFFECTS

3.4.1. Oral Exposures

3.4.1.1. Primary Target(s)

1. CNS and Kidney: Both the CNS and kidneys are affected by inorganic mercury. The toxic effects may occur with acute, subchronic, or chronic exposure depending on the exposure level and the resulting body burden of mercury. Animal data suggests that the renal effects may be immunologically mediated. The CNS, especially during prenatal and postnatal development, is the primary target organ for methyl mercury.

3.4.1.2. Other Target(s)

1. Cardiovascular system: acute exposure to mercury has caused cardiovascular collapse and some effects associated with acrodynia involve cardiovascular responses.

2. Immune system: As noted in section 3.4.1.1., animal data suggests that the nephrotoxic effects of mercury may, in part, be the result of mercury-induced immunological effects.

3. Skin: Skin rashes and hyperkeratosis are involved in acrodynia, a response to mercurous chloride (calomel).

3.4.2. Inhalation Exposures

3.4.2.1. Primary Target(s)

1. CNS and Peripheral Nervous System: The critical target organs for inhalation exposure to elemental mercury vapor are the CNS and the peripheral nervous system.

2. Kidney: Inorganic mercury salts will primarily affect the kidneys.

Definitive data were unavailable regarding the target organ for inhalation exposure to organic mercury compounds but, as for oral exposure, it is likely that the CNS would be the primary target organ.

3.4.2.2. Other Target(s)

1. Respiratory System: Exposure to high concentrations of metallic mercury vapor may cause irritation of the respiratory system.

2. Cardiovascular System: Exposure to high concentrations of metallic mercury vapor may also affect the cardiovascular system.

3. Gastrointestinal Tract: Exposure to high concentrations of metallic mercury vapor may also affect the gastrointestinal systems, probably as a result of swallowing mercury that has been removed from the airways by the mucociliary escalator.

4. CARCINOGENICITY

4.1. ORAL EXPOSURE

4.1.1. Human

Definitive data regarding the potential carcinogenicity of mercury and mercury compounds in humans was unavailable.

4.1.2. Animal

Definitive data regarding the potential carcinogenicity of mercury and mercury compounds in animals was unavailable.

4.2. INHALATION EXPOSURE

4.2.1 Human

Definitive data regarding the potential carcinogenicity of mercury and mercury compounds in humans was unavailable. An equivocal study by Janicki et al. (1987) reported an association between exposure to mercury-containing fungicides and leukemia.

4.2.2. Animal

Definitive data regarding the potential carcinogenicity of mercury and mercury compounds in humans was unavailable.

4.3. OTHER ROUTES OF EXPOSURE

No information was available regarding the potential carcinogenicity of mercury or mercury compounds by other routes of exposure.

4.4. EPA WEIGHT-OF-EVIDENCE

Inorganic mercury:

Classification D - Not classifiable as to human carcinogenicity
Basis - No human data available. Animal and supporting data are inadequate.
(U.S. EPA, 1991b)

Methyl mercury:

Methyl mercury has not been evaluated by the U.S. EPA for evidence of human carcinogenic potential.

4.5. CARCINOGENICITY SLOPE FACTOR

None have been calculated

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LEAD

The absorption of lead from the gastrointestinal tract is dependant on a number of factors including age and nutritional state. Adults absorb between 5-15% of an ingested dose and retain less than 5% of the absorbed dose. Children may absorb and retain as much as 42% of an ingested dose. Absorption of inhaled lead is relatively complete (ref. 1).

Target organs for the toxic actions of lead include the central nervous system, blood forming tissues, the gastrointestinal system and the reproductive system. Of these, the CNS effects are of most concern (ref. 1). Blood lead levels have been used as an indicator of exposure and a number of toxic endpoints have been correlated with these levels. The following biological monitoring levels may be indicative of exposure to lead: (ref. 4)

- -Blood lead levels greater than 9ug/dl.
- -Urine creatinine levels greater than 65ug/g.
- -Blood zinc protoporphyrin levels >35 ug/dl.

Children appear to be particularly susceptible to the neurotoxic effects of lead. Neurobehavioral development abnormalities may occur at low blood lead levels. (ref. 2)

Several of the soluble lead salts have been shown to produce renal tumors in rodent bioassays. Epidemiological evidence from human occupational exposures was inadequate to demonstrate a clear association between lead exposures and cancer. Based on these data, the EPA has classified lead as a B2 carcinogen (ref.2). Because of the uncertainties associated with the lead carcinogen risk assessment, the EPA recommended that numerical estimates of risk from lead exposure be avoided (ref.2).

The EPA is currently developing guidelines for performing environmental risk assessments involving lead. As an interim measure, the EPA is suggesting the use of a Centers for Disease Control (CDC) document which recommends that soil lead levels between 500 ppm - 1000 ppm are safe levels, protective of the neurological effects in children (ref. 3). These values only address soil ingestion which is probably the most important pathway when dealing with children. (ref.3) In terms of air lead, the EPA promulgated a NAAQS of 1.5 ug/m^3. This level is also undergoing extensive review. In the absence of toxicity values, the CDC recommendations concerning soil lead concentrations and the NAAQ primary air standard will be used to partially quantify health risks in the current evaluation.

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