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**CHRONIC AND SUBCHRONIC, SYSTEMIC AND CARCINOGENIC, ORAL
AND INHALATION TOXICITY INFORMATION FOR 2-HEXANONE,
MAGNESIUM, TRIBUTYL PHOSPHATE, AND MIXED XYLENES. ORAL
AND DERMAL ABSORPTION FACTORS FOR MULTIPLE CHEMICALS.
(OU4, OU1 & OU2 RI REFERENCE)**

07/21/93

**DOLLARHIDE VANLEEUWEN/EPA
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REPORT**



Pick up for Dr. J Price
Fernald

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF RESEARCH AND DEVELOPMENT
ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
CINCINNATI, OHIO 45268

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MEMORANDUM:

DATE: July 21, 1993

SUBJECT: Chronic and Subchronic, Systemic and Carcinogenic, Oral and Inhalation Toxicity Information for 2-Hexanone (Methyl n-Butyl Ketone, CAS No. 591-78-6), Magnesium (CAS No. 7439-95-6), Tributyl Phosphate (CAS No. 126-73-8) and Mixed Xylenes (CAS No. 1330-20-7). Oral and Dermal Absorption Factors for Multiple Chemicals (FEMP O.U.#4/Fernald, OH)

FROM: Joan S. Dollarhide *Joan S Dollarhide*
Associate Director
Superfund Health Risk Technical Support Center
Chemical Mixtures Assessment Branch

TO: Pat VanLeeuwen
U.S. EPA
Region V

This memorandum is in response to your request for chronic and subchronic, systemic and carcinogenic, oral and inhalation toxicity values for contaminants found at the FEMP O.U. #4 in Fernald, Ohio.

We are currently preparing a provisional RfC for 2-hexanone; however, we were not able to complete this work within the short time frame for this request. If you are interested in seeing this information when it is complete, please let me know.

Attached please find the following information:

Attachment 1: Risk Assessment Issue Paper for: Derivation of a Provisional RfD for 2-Hexanone (Methyl n-Butyl Ketone, CAS No. 591-78-6)

Attachment 2a: Risk Assessment Issue Paper for: Systemic Toxicity Information for Magnesium (CAS No. 7439-95-4)

Attachment 2b: Risk Assessment Issue Paper for: Evaluation of Carcinogenicity of Magnesium (CAS No. 7439-95-4)

Attachment 3: Provisional Chronic RfD and Oral Slope Factor for Tributyl Phosphate (CAS No. 126-73-8)

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Attachment 4: Risk Assessment Issue Paper for: Subchronic
Inhalation Toxicity For Mixed Xylenes (CAS NO.
1330-20-7)

We were unable to provide systemic or carcinogenic information for butanoic acid methyl ester, 3-methyl-2-butanone or 2-nitrophenol and we did not address those contaminants for which direction was already provided by Region V (i.e., iron, acenaphthylene, endosulfan-I and endosulfan-II) (see original request to STSC).

Attachment 5: Oral and Dermal Absorption Information for
Multiple Chemicals.

We are forwarding oral and dermal absorption information to you that we have previously provided for other sites. Thus, we have not undertaken any additional research for your request. Moreover, due to the nature of the original requests, the information may or may not apply to your site situation.

Please realize in some cases we have provided more than one oral or dermal assessment for a particular chemical. It is important to recognize that inconsistencies in the information may reflect uncertainties in the data or variation due to different dates of completion. Dates of origin of the information are noted in parentheses at the top of the issue paper. It is left to the Regions discretion as to which assessment to apply. Please note that the information provided is provisional and therefore has not been through the Agency's review process. If you have any questions, please do not hesitate to call.

Also attached (Attachment 6) please find a memorandum from Karen Hammerstrom of the Exposure Assessment Group which was prepared for a risk assessment done for American Chemical Services. Karen's memorandum discusses default values that might be appropriate for chemical classes if Region V feels that this is a more appropriate approach.

Please feel free to contact the Superfund Technical Support Center at (513) 569-7300 if you need additional information.

Attachments

cc: E. Moran (Region V-RTIC)
J. Prince (FERMCO)
C. Sonich-Mullin (ECAO-Cin)

Attachment 1

(July, 1993)

**Risk Assessment Issue Paper for:
Derivation of a Provisional RfD for
2-Hexanone (Methyl n-Butyl Ketone, CAS No. 591-78-6)**

We have confirmed that no RfD values for 2-hexanone are available on updated versions of IRIS (U.S. EPA, 1993a), nor is this chemical under discussion by the RfD/RfC Work Group (U.S. EPA, 1993b). No new information is provided in the HEAST (U.S. EPA 1992a), NTP Status Reports (NTP, 1993a,b), or Drinking Water Regulations and Health Advisories (U.S. EPA 1992b). The following literature searches were also conducted: TOXLINE (1991 - present), TSCATS, HSDB, and RTECS. No new information was located.

Review documents available for 2-hexanone include a Health and Environmental Effects Document (U.S. EPA, 1990), a Toxicological Profile (ATSDR, 1992), and a toxicity review by Bos et al. (1991). These documents were examined for information pertinent to derivation of an oral RfD for 2-hexanone. Computer searches of TOXLINE (1988-1991), RTECS, HSDB, and TSCATS were performed in 1991 and inspected for relevant information; update searches of TOXLINE (1991-1993, oral and inhalation), TSCATS, RTECS, and HSDB were performed in April, 1993.

This chemical is not listed on IRIS (U.S. EPA, 1993a), the RfD/RfC Status Report (U.S. EPA, 1993b), the Drinking Water Regulations and Health Advisories list (U.S. EPA, 1992b), or the NTP Status Reports (NTP, 1993a, b). The HEAST (U.S. EPA, 1992a) states that data are inadequate for quantitative risk assessment for 2-hexanone.

The nervous system appears to be the primary target of 2-hexanone, with the critical effect being peripheral neuropathy (ATSDR, 1991; U.S. EPA, 1990). This effect was observed in humans following inadvertent industrial exposure, and has been repeatedly demonstrated in laboratory animals as well. The related compound, n-hexane, also produces peripheral neuropathy (U.S. EPA, 1989). It has been shown that n-hexane and 2-hexanone share metabolic pathways, and that the active metabolite for both compounds is 2,5-hexanedione (ATSDR, 1991; U.S. EPA, 1989, 1990). There is evidence that the testes may also be a target of 2-hexanone toxicity (ATSDR, 1991; U.S. EPA, 1990). Atrophy of testicular germinal epithelium has been reported in rats exposed by inhalation (700 ppm for 11 weeks) and oral gavage (660 mg/kg, 5 days/week for 10 weeks). Development has not been studied using oral exposure, but a developmental study using inhalation exposure (Peters et al., 1981) reported behavioral alterations in the offspring of pregnant rats exposed to 1000 ppm of 2-hexanone

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throughout gestation; significantly reduced number and weight of live offspring were reported at 2000 ppm. Decreased body weight gain in dams was also noted at these concentrations.

Although the toxicity of 2-hexanone is fairly well characterized, the database for oral exposure is weak. Only five studies of subchronic/chronic oral exposure were located, and two of these are clearly unsuitable for use in risk assessment due to inadequate reporting of methods and/or results (Abdel-Rahman et al., 1978; Krasavage et al., 1979). As for the remaining studies, two incorporated only a single dose level (Eben et al., 1979; Krasavage et al., 1980) and the other used dose groups consisting of only 5 animals each (Carnegie-Mellon Institute of Research, 1977a, 1977b). Due to the weakness of the database, U.S. EPA (1990) declined to derive an RfD for 2-hexanone. However, this document omitted discussion of several of the available studies (Carnegie-Mellon Institute of Research, 1977a, 1977b; Eben et al., 1979).

Among the three adequately reported studies, the study by Krasavage et al. (1980) was not useful for risk assessment because severe neurological effects (hindlimb paralysis) were produced in rats at the only dose level tested (660 mg/kg by gavage 5 days/week for 10 weeks). However, it was possible to derive a provisional RfD for 2-hexanone based on the studies by the Carnegie-Mellon Institute of Research (1977a, 1977b) and Eben et al. (1979). In the Carnegie-Mellon study, which is also available in the published literature in the form of an abstract (Homan and Maronpot, 1978), groups of 5 female Wistar rats were exposed to 2-hexanone at concentrations of 0.65% or 1.3% (saturated) in the drinking water for 120 days. The researchers determined that the rats in the low and high dose groups received average doses of 480 and 1010 mg/kg/day, respectively. The treated rats were compared to 2 separate control groups, each consisting of 5 rats. Endpoints examined in this study were food and water intake, body weight, general appearance and behavior, neurological evaluation (in which balance, strength, coordination, and behavior were assessed according to predetermined criteria), organ weights, and gross and microscopic pathology (comprehensive examination).

Water intake was lower in treated rats (≈ 17 ml/day) than in controls (≈ 30 ml/day). The difference was not statistically significant, but it should be noted that the small group sizes used in this study limit the resolving power of statistical tests. There was no effect on food intake, but body weight gain was significantly ($p < 0.001$) reduced by $\approx 50\%$ in the low dose group and $\approx 75\%$ in the high dose group. The authors observed "unequivocal neurological deficits" in the treated rats, including weakness, incoordination, and muscle wasting

(especially of the hind limbs). Although neurological effects were seen in both treatment groups, they appeared to be transitory and relatively mild in the low dose group. A statistically significant ($p < 0.05$) neurological deficit was found only for high dose rats exposed for 110 days.

Organ weight changes were seen in the liver and kidney. Liver weight was significantly ($p < 0.001$) decreased by $\approx 20\%$ in high dose rats, although the ratio of liver weight to body weight was unchanged. For the kidney, absolute weight remained unchanged, while relative weight increased ($p < 0.001$) by $\approx 33\%$ in the low dose rats and $\approx 50\%$ in the high dose rats. Gross pathological examination found mild atrophy of the hind limb skeletal muscles in 2/5 low dose rats and more severe atrophy of skeletal muscle (not limited to hind limbs) in 4/5 high dose rats. This condition was not seen in the controls. Histological examination of the gastrocnemius revealed microscopic atrophy in 3/5 low dose rats and 3/5 high dose rats (atrophy detected grossly in a fourth rat was not present in the gastrocnemius). The difference from controls (0/5 in each group) was not statistically significant. Also detected by histopathological examination was peripheral neuropathy (predominantly myelin clumping and axonal swelling of the sciatic nerve), which was found in 4/5 low dose rats and 5/5 high dose rats. The incidence of peripheral neuropathy was significantly ($p < 0.05$) elevated over controls in both groups (0/5 each). No treatment-related histopathological lesions were found in other organs or tissues.

In the study by Eben et al. (1979), groups of 60 male Wistar rats were given 400 mg/kg/day of 2-hexanone (in emulsion with Cremophor EL and water) by daily gavage for 40 weeks. The study did not include quantitative neurological evaluation or histopathological examination, but did include informal neurological observation. At this dose level, the only grossly visible neurological effect was a transitory weakness in the hind limbs during the middle part of the experiment. This observation is consistent with the results of the 480 mg/kg/day group in the Carnegie-Mellon study, as is the finding of 50% lower body weight gain in treated rats than in controls in this study. This study also investigated effects on the liver and kidney, as shown by measurements of SGOT and SGPT, and plasma urea and creatinine, respectively, but failed to find any difference from controls.

DERIVATION OF ORAL RfD

The Carnegie-Mellon study, which included detailed evaluation of the critical neurological effects, demonstrated a graded response between the two dose levels tested. Although a NOAEL was not identified, the relative subtlety of the effects observed at the LOAEL of 480 mg/kg/day suggests that this value

might reasonably be used in risk assessment. The study by Eben et al. (1979) produced a free-standing LOAEL of 400 mg/kg/day, based on observations consistent with those reported in rats exposed to 480 mg/kg/day in the Carnegie-Mellon study. Considering both studies together, it appears reasonable to use the overall LOAEL of 400 mg/kg/day as the basis for RfD derivation. Applying the maximum uncertainty factor of 10,000 (reflecting five areas of uncertainty: variation within and between species, use of a LOAEL, extrapolation to chronic duration, and weakness of the database) produces an oral RfD of 0.04 mg/kg/day for 2-hexanone.

Confidence in this RfD is low due to low confidence in both the critical studies and the database as a whole. Confidence in the critical studies is low because of important deficiencies in these studies. The Carnegie-Mellon study employed only two dose levels and included very small numbers of test animals. The study by Eben et al. (1979) used only one dose level and failed to include monitoring of subtle manifestations of the critical neurological effect (i.e. histopathology and neurological evaluation). Confidence in the database is low because oral studies of chronic duration are not available, existing subchronic oral studies are inadequate to provide supporting data, and oral studies of reproduction and development have not been conducted.

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Attachment 2a

Risk Assessment Issue Paper for:
Systemic Toxicity Information for
Magnesium (CASRN 7439-95-4)

Provisional Oral RfD

Magnesium intoxication is most likely observed as a result of excessive intake when administered as a therapeutic agent. Magnesium is commonly used as a gastric antacid in the treatment of reflux esophagitis and peptic ulcer (Harvey, 1985). Magnesium hydroxide is the usual preparation since due to its poor water solubility the free concentration of OH^- is too low for the $\text{Mg}(\text{OH})_2$ to be corrosive. Magnesium carbonate is also used as antacid. Milk of magnesia is the only single-entity preparation of $\text{Mg}(\text{OH})_2$. Magnesium hydroxide is frequently incorporated with $\text{Al}(\text{OH})_3$ in a variety of products. Magnesium hydroxide is also used as a laxative (Brunton, 1985); this property is attributed to an osmotic effect, however, Mg^{2+} also stimulates the secretion of cholecystokinin, which may contribute to the increased motor activity. Other therapeutic uses of magnesium include the treatment of seizures associated with acute nephritis and with eclampsia of pregnancy, and as a local agent in the treatment of skin burns from hydrofluoric acid.

As indicated by Sutton and Dirks (1986), hypermagnesemia is an uncommon clinical problem. Since healthy individuals can excrete excess magnesium efficiently from the extracellular fluid into the urine, hypermagnesemia is generally confined to circumstances in which the load of magnesium delivered to the extracellular fluid is extremely high, or in which renal magnesium clearance is reduced.

The main causes of hypermagnesemia, as reviewed by Rude and Singer (1981), are:

1. Excessive intake. Oral ingestion of magnesium has seldom been reported to result in magnesium intoxication without coexisting renal failure. Rectal administration of magnesium may, without apparent cause, induce hypermagnesemia in subjects with normal renal function.

2. Impaired excretion. This is usually seen in patients with chronic renal failure who are receiving magnesium-containing antacids, enemas, or infusions, and whose glomerular filtration rate falls below 10-30 ml/min (normal GFR is approximately 120 ml/min in adult males).

3. Parenteral administration. Hypermagnesemia can occur due to inadequate monitoring of the plasma magnesium concentration as in the treatment of toxemia of pregnancy.

4. Other causes. Mild to moderate hypermagnesemia has been reported in lithium ingestion, hypothyroidism, mild-alkali syndrome, viral hepatitis, and Addison's disease.

The normal plasma concentration of magnesium ranges between 1.3 and 2.5 mEq/L. Early nonspecific manifestations of magnesium intoxication that may appear with plasma magnesium concentrations of 3-9 mEq/L include nausea, vomiting, and cutaneous flushing. Other effects and clinical manifestations of excess magnesium are impaired neuromuscular function and disappearance of deep tendon reflexes. Paralysis of voluntary muscles may occur with plasma magnesium concentrations of 10 mEq/L or greater. Hypotension and bradycardia are among cardiovascular changes associated with hypermagnesemia. Complete heart block may occur at plasma levels greater than 15 mEq/L.

Based on the best information available at the present time, we have derived a chronic oral reference dose (RfD) of 9.7 mg/kg/day. The derivation of this reference dose was based on the pharmacokinetic considerations detailed below.

The RfD is based on the generally accepted fact that magnesium plasma levels greater than 4 mEq/L are known to cause adverse health effects in humans (Mordess and Wacker, 1978). Therefore, the RfD was derived by calculating the dose of magnesium ingested daily that will result in such a steady-state plasma level of 4 mEq/L. As indicated above, the normal plasma concentration of magnesium ranges between 1.3 and 2.5 mEq/L. For the purpose of the derivation of the RfD an average value of 1.9 mEq/L (22.8 mg/L) was assumed.

The major excretory pathway for magnesium is renal; oral and intravenous loads are rapidly eliminated in the urine (Mordess and Wacker, 1978). Based on data obtained in experimental animals, it appears that tubular secretion plays a minor role in the renal handling of magnesium (Massry, 1977).

The elimination rate constant (k_e) for magnesium was derived as follows:

$$\begin{aligned}C_{Mg} &= k_e \times V_d \\E_{Mg} &= [Mg]_p \times C_{Mg} \\k_e &= E_{Mg} / \{ ([Mg]_p) (V_d) \}\end{aligned}$$

where

- C_{Mg} = plasma clearance of magnesium (L/day)
 k_e = elimination rate constant for magnesium (days⁻¹)
 V_d = volume of distribution of magnesium (147 L for an adult male). This is calculated by dividing the total exchangeable pool of magnesium (3360 mg/L) by the normal plasma concentration of magnesium (22.8 mg/L) (Sutton and Dirks, 1986)
 E_{Mg} = daily magnesium excretion (96 mg/day)
 $[Mg]_p$ = steady state plasma magnesium concentration (22.8 mg/L)

therefore,

$$k_e = 96 / [22.8 \times 147] = 0.029/\text{day}$$

The intake (absorbed dose) that will result in a steady-state plasma level of 4 meq/L (48 mg/L) was calculated as follows:

$$I = ([Mg]_p) (V_d) (k_e) / BW$$

$$I = (48 \text{ mg/L}) (147 \text{ L}) (0.029/\text{day}) / (70 \text{ kg})$$

$$I = 2.9 \text{ mg/kg/day}$$

where

I = daily intake associated with steady state plasma level of 48 mg/L

BW = body weight of adult male (kg)

The oral absorption efficiency for magnesium is reported as 30% (Carson et al., 1986). The oral intake (administered dose) of magnesium below which no adverse effects should be expected in the normal human population is therefore, 9.7 mg/kg/day, i.e.:

$$RfD = I / (0.3)$$

$$RfD = (2.9 \text{ mg/kg/day}) / (0.3) = 9.7 \text{ mg/kg/day}$$

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One should keep in mind, however, that the bioavailability of magnesium from the different environmental media will undoubtedly vary.

The Recommended Daily Allowance for magnesium is 4.5 mg/kg/day (NRC, 1989), and is approximately 50% lower than the oral RfD calculated above. We must point out that the RfD of 9.7 mg/kg/day may be an over conservative number because the k_e increases with increasing plasma concentration. Thus a person could possibly require greater than 9.7 mg magnesium/kg/day to produce a steady-state plasma magnesium level of 4 mEq/L. No information was located regarding changes in magnesium excretion as a function of a wide range of magnesium plasma levels.

We were able to identify a recent study by Kurata et al. (1989) in which female B6C3F₁ mice fed a diet that provided 466 mg Mg⁺⁺/kg/day for 96 weeks had depressed weight gain throughout the treatment period. This depressed weight gain was observed even though food consumption was normal. Urinary, hematological or clinical chemistry parameters were not affected by treatment. Examination of the major tissues and organs revealed no effects attributed to magnesium treatment. If the dose of 466 mg/kg/day is considered a LOAEL, then applying an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for the use of a LOAEL, and 10 to protect sensitive human subpopulations) results in a chronic oral RfD of 0.5 mg/kg/day. This is approximately 20 times lower than the RfD derived above from human data.

The RfD that was derived, 9.7 mg/kg/day, is conservative largely because the k_e (elimination rate constant) for magnesium increases with increasing intake and/or plasma concentration. Therefore, in healthy humans, excessive intake of magnesium does not necessarily lead to increased plasma levels of magnesium. The physiological basis for the increased k_e is decreased net reabsorption of magnesium in the renal tubule. This increase in the filtered load of magnesium is completely excreted (Rude et al., 1980).

In conclusion, based on human data, a provisional oral RfD of 9.7 mg/kg/day was derived which is approximately two times higher than the RDA for adults.

It is not known whether or not the renal handling of magnesium after sudden and intermittent loads will be the same than after a prolonged and continuous intake.

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Attachment 2b

Risk Assessment Issue Paper for: Evaluation of Carcinogenicity of Magnesium (CASRN 7439-95-4)

INTRODUCTION

The following literature searches were performed: TOXLINE (1965-1991) and MEDLINE (1966-1980). Magnesium has not been the subject of an ATSDR profile or of any EPA documents prepared by OHEA. Magnesium is not listed on IRIS (U.S. EPA, 1993a) or the HEAST (U.S. EPA, 1992), is not under consideration by the CRAVE Work Group (U.S. EPA, 1993b) and has not been selected for study by the NTP (1991).

ACGIH (1991) recommended TLV-TWAs of 10 mg/m^3 for magnesite [$\approx (\text{MgCO}_3)_x \cdot \text{Mg}(\text{OH})_2 \cdot 5\text{H}_2\text{O}$] (OSHA, 1989), and 10 mg/m^3 for magnesium oxide fume. Documentation is not yet available for the TLV-TWA for magnesite; the TLV-TWA for magnesium oxide fume is "believed adequate to protect workers from any adverse health effects" (ACGIH, 1986). OSHA (1989) established a final rule TWA-PEL for magnesite of 15 mg/m^3 for total particulates, and 5 mg/m^3 for the respirable fraction, to protect workers against skin, mucous membrane and other physical irritation. For magnesium oxide fume, the final rule TWA-PEL is 10 mg/m^3 for total particulates and 5 mg/m^3 for the respirable fraction, which is expected to substantially reduce the risks of metal fume fever, leukocytosis, and, perhaps, chronic respiratory disease due to magnesium oxide fumes in the workplace. NIOSH (1990) judged the documentation inadequate for supporting an REL for magnesium oxide fume. None of these occupational exposure limits indicate any concern over carcinogenicity.

Early in this task it became apparent that magnesium exists in several different natural and processed forms, including natural magnesite (approximate formula in previous paragraph), several types of processed magnesite (MgO) and magnesia (MgO), several organic (e.g., acetate, citrate, palmitate) and inorganic salts (e.g., hydroxide, chloride, phosphate, nitrate) and complex salts with other metals (e.g., borate, dichromate, stannate). In addition, magnesium is a major component of asbestos and other magnesium silicate fibers (Hawley, 1981). Careful screening of the literature searches revealed that the effects of magnesium on biological systems depends largely on the form of magnesium involved.

Although practically insoluble in water, $\text{Mg}(\text{OH})_2$ will dissociate yielding Mg^{2+} in dilute acid, such as found in the

stomach (Budavari, 1989). Therefore, this evaluation will address all inorganic salts of magnesium that yield Mg^{2+} and for which the anion is not expected to contribute to the toxicity of the salt. The other forms of magnesium listed in the previous paragraph are not addressed in this evaluation.

CARCINOGENICITY TO HUMANS

Human cancer incidence studies are limited to a mortality study of a cohort of 2391 male workers employed for ≥ 1 year during 1953-1984 in a Norwegian magnesium metal-producing plant, and observed from 1953-1984 (Heldaas et al., 1989). The reference group was a constructed Norwegian population with an identical age distribution; expected numbers of deaths were based on national five year age-specific death rates. The workers were subdivided into ten exposure categories based on the job classifications in which they worked. At least four exposure categories involved exposure to one of at least three compounds of magnesium (MgO , $MgCl_2$, and unspecified), as well as to coal dust, asbestos, chlorinated aromatic compounds (hexachlorobenzene predominated), chlorine gas, sulfur dioxide, heat or strong electromagnetic fields.

A total of 152 cancer-related deaths occurred in the total cohort, compared with 132.6 expected. Statistically significantly increased relative risk (RR) was observed for cancer of the lung (RR = 1.8), lip (RR = 2.6) and stomach (RR = 1.6). Among workers exposed to magnesium, excess deaths due to lung cancer (RR = 1.7, statistical significance unclear) were observed in only one of four categories, involving exposure to MgO and coal dust (Heldaas et al., 1989). This study has limited value in the cancer hazard assessment of magnesium, because the workers were exposed to a multitude of known and suspected carcinogens and because exposures were not quantified. The study represents inadequate evidence for carcinogenicity in humans.

According to Blondell (1980), a report showing an inverse relationship between water hardness and cancer incidence, and another report showing reduced risk of cancer in persons living at high altitudes suggest an anticarcinogenic effect for magnesium. Magnesium and calcium are the principal causes of hardness in water, and living at high altitudes may increase blood pH, which may favor binding of magnesium to cell membranes. In addition, cancer mortality rates tend to be higher in regions with lower soil magnesium levels.

CARCINOGENICITY TO ANIMALS

Blondell (1980) also reviewed animal studies that support an anticarcinogenic effect of magnesium. In two separate studies, rats on low magnesium diets showed increased incidence of lymphoma, or developed chronic myelogenous leukemia, an unusual tumor in the rat, after 5-12 months of magnesium deprivation (Battifora et al., 1968). In mice, supplemental magnesium in the drinking water reduced the incidence of cancer induced by dermal application or parenteral injection of polyaromatic hydrocarbons (PAH). Blondell (1980) hypothesized that intracellular magnesium is important in the fidelity of DNA replication and that cell membrane-bound magnesium may retard cancer-initiating processes.

In the only dose-response study of magnesium-induced carcinogenicity in animals, Kurata et al. (1989) added 0, 0.5 or 2% $MgCl_2 \cdot 6H_2O$ to a commercial diet (presumably containing a nutritionally adequate level of magnesium) for feeding to groups of 50 male and 50 female 6-week-old B6C3F1 mice for 96 weeks. Dietary levels were selected based on the results of a 13-week study in which no effects were observed in mice fed a diet containing 2.5% added $MgCl_2 \cdot 6H_2O$, but decreased body weight and increased vacuolation of the kidney were observed in males fed a diet containing 5% $MgCl_2 \cdot 6H_2O$. Control diet was fed to all groups for an additional 8 weeks before sacrifice. Parameters of toxicity evaluated included general appearance and behavior, survival, food and water consumption, body weight, urinalysis, extensive hematology and clinical chemistry, necropsy, relative organ weights and histopathologic examination of ≈ 19 tissues and all macroscopic lesions.

The only biologically significant effects attributed to added magnesium chloride were decreased body weight ($\approx 25\%$ at termination) in the high-dose females starting at week 8, increased absolute and relative brain weight and increased relative heart and kidney weight. High-dose females consumed slightly more feed than control females. The incidence of malignant lymphoma/leukemia was slightly, but not significantly increased in treated mice of both sexes (particularly females), compared with controls, but the trend in the females was not dose related. The incidence of hepatocellular carcinomas in male mice decreased in a dose-related manner; the difference from the controls was significant ($p < 0.05$) in the high-dose males (Kurata et al., 1989). The effect on body weight suggests that the maximum tolerated dose (MTD) was attained in the females, but there is no indication that the MTD was attained in the males.

GENOTOXICITY

Ashby and Ishidate (1986) evaluated the clastogenicity of magnesium chloride in cultures of Chinese hamster lung fibroblasts. Positive results, predominantly chromatid gaps, breaks and exchanges, were observed at 8.0 and 12.0 mg $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}/\text{ml}$, but not at ≤ 4 mg/ml.

Sideris et al. (1988) showed that incubation of Chinese hamster V-79 cells in increasing concentrations of magnesium nitrate (10^{-6} - 10^{-3} M) progressively increased the thermostability of DNA, presumably because Mg^{2+} bound to the phosphate moieties of the DNA. Incubation of V-79 cells with 10^{-4} M magnesium nitrate did not induce strand breaks, as indicated by the alkaline elution test, and incubation with 10^{-4} or 10^{-3} M magnesium nitrate did not increase the frequency of mutation to 8-azaguanine resistance.

Amacher and Paillet (1980) tested the ability of Mg^{2+} from $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ to induce mutations in mouse lymphoma L5178/TK⁺ cells in culture. Test concentrations were 5.7-18.1 mg Mg^{2+}/ml (2.81×10^{-2} - 8.90×10^{-2} M). The results were negative.

Sirover and Loeb (1976) investigated the effect of Mg^{2+} from MgSO_4 to decrease the rate and fidelity of DNA synthesis in an in vitro system using DNA polymerase, template, Mg^{2+} (required cofactor in the system) and complementary and anticomplementary deoxynucleoside triphosphates labeled with different radioactive isotopes. Concentrations of 4-10 mM had no effect on either the rate or fidelity of DNA synthesis.

WEIGHT OF EVIDENCE CLASSIFICATION

Human data are limited to circumstantial evidence suggesting a anticarcinogenic role for magnesium (Blondell, 1980), and an epidemiologic study of cancer deaths in a magnesium metal-producing plant (Heldaas et al., 1989). Although there was an association between exposure to magnesium and increased risk of lung cancer in the epidemiology study, interpretation of the study was confounded by exposure to other known and suspected carcinogens. Applying the U.S. EPA (1986) guidelines to the human data, the evidence for carcinogenicity to humans is considered inadequate.

The animal data also suggest an anticarcinogenic role for magnesium. Magnesium deficiency increased the incidence of cancer in rats, and supplemental magnesium reduced the incidence of PAH-induced cancers in mice (Battifora et al., 1968; Blondell,

1980). In the only dose-response cancer study with magnesium in animals, no significant increase of cancer incidence was seen in a 96-week drinking water experiment in mice. The MTD was attained in the females, although probably not in the males, the test substance was given to adequately sized groups of both sexes of an appropriate animal model for a sufficient duration, and sufficient animals survived to be at risk for late developing tumors. Collectively, the animal data are considered inadequate evidence for carcinogenicity in humans.

On the basis of inadequate evidence for carcinogenicity in humans and animals, inorganic magnesium salts that yield Mg^{2+} in biological systems are classified in U.S. EPA (1986) weight-of-evidence Group D: not classifiable as to human carcinogenicity.

DERIVATION OF ORAL SLOPE FACTOR

The U.S. EPA (1986) guidelines state that slope factors are not derived for weight-of-evidence Group D chemicals; therefore, no attempt is made to derive an oral slope factor for inorganic salts of magnesium.

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Attachment 3

- Risk Assessment Issue Paper for:
Provisional Chronic RfD and Oral Slope Factor for
Tributyl Phosphate (CAS No. 126-73-8)

INTRODUCTION

No chronic RfD or slope factor for tributyl phosphate were available on IRIS (U.S. EPA, 1992a), and tributyl phosphate was not listed on the RfD/RfC or CRAVE status reports (U.S. EPA, 1992b,c). No documents for tributyl phosphate were listed in the CARA list (U.S. EPA 1991a), NTP Status Report (NTP, 1992), HEAST (U.S. EPA, 1992d), or Drinking Water Regulations and Health Advisories (U.S. EPA, 1991b). No ATSDR documents regarding tributyl phosphate were available.

To identify research reports pertinent to the derivation of a chronic RfD and oral slope factor for tributyl phosphate, the HSDB, RTECS, and TSCATS databases were reviewed; in addition, a computer search of the literature was conducted (TOXLINE, January, 1981 - May, 1992). (SRC, 1986) was used to identify pertinent research reports, but was not used as a primary or secondary source.

SYSTEMIC TOXICITY

In an epidemiological study, 12 workers exposed to fumes containing tributyl phosphate and other compounds were evaluated for serum monocyte levels, as determined by monocyte nonspecific esterase staining activity (Mandel et al., 1989). Exposure levels and length of exposure to tributyl phosphate were not reported. Monocyte levels were similar between the general population and workers exposed to tributyl phosphate.

Sprague-Dawley rats (15/sex/dose group; approximately 44 days of age) were treated with 0, 8, 40, 200, 1000, or 5000 ppm tri-n-butyl phosphate (purity >99%) in the diet for 13 weeks (FMC, 1985); the dose levels, calculated from body weight and food consumption data in the study, were 0, 1, 3, 14, 68, and 360 mg/kg/day for males and 0, 1, 3, 16, 81, and 423 mg/kg/day for females. The following parameters were used to assess toxicity: mortality, clinical signs, body weight gain, food consumption, hematology, serum chemistry, ophthalmology, organ weights (brain, heart, liver, kidneys, gonads, and adrenals), gross necropsy (all major tissues and organs), and histology (all major tissues and organs in control and high-dose groups; liver and urinary bladders in all groups). An interim sacrifice (5 rats/sex/dose group) was performed at 45 days, and blood samples were obtained

for hematological and serum chemistry analysis; the remaining 10 rats/sex/dose group were examined at terminal sacrifice. The treatment had no adverse effects with respect to mortality, ophthalmology, interim hematology, or gross necropsy. Abdominogenital staining was observed sporadically in males and females fed 1000 or 5000 ppm. Body weight gain was significantly ($p < 0.05$) decreased in high-dose males (14%) and females (13%). Food consumption was significantly ($p < 0.05$) decreased throughout the study in high-dose males (9%) and sporadically in high-dose females (6%). A significant ($p < 0.05$) increase in activated partial thromboplastin time was observed in high-dose males at termination. SGPT values were significantly ($p < 0.05$) increased in high-dose males at interim sampling and high-dose females at termination. SGGT values were significantly ($p < 0.05$) increased in males at 1000 and 5000 ppm and females at 5000 ppm at the interim sampling time, and in high-dose males and females at termination. Significant ($p < 0.05$) increases were observed at terminal sacrifice in cholesterol levels in high-dose females, and in albumin and calcium levels in high-dose males. Significant ($p < 0.05$) increases in liver/brain weight ratios were observed in 1000 and 5000 ppm males, and in 5000 ppm females. No histological abnormalities were observed in livers of treated rats. Generalized transitional-cell hyperplasia was observed in the urinary bladders of all 1000 and 5000 ppm males, and in 8/9 of the 5000 ppm females; this effect was not observed in rats in other groups. No evidence of malignant or preneoplastic alterations in urinary bladders was observed. This study identifies a NOAEL of 200 ppm (14 mg/kg/day) and a LOAEL of 1000 ppm (68 mg/kg/day) for urinary bladder cell hyperplasia in rats treated with tri-n-butyl phosphate in the diet for 13 weeks.

CD-1 mice (15/sex/dose group; approximately 42 days of age) were treated with 0, 500, 2000, or 8000 ppm tributyl phosphate (purity 99.7%) in the diet for 13 weeks (Bio/dynamics Inc., 1991a); the dose levels, calculated from body weight and food consumption data in the study, were 0, 96, 383, or 1479 mg/kg/day for males and 0, 119, 462, or 1769 mg/kg/day for females. The following parameters were used to assess toxicity: mortality, clinical signs, ophthalmology, body weight gain, food consumption, hematology, serum chemistry, organ weights (brain, heart, liver, kidneys, gonads, and adrenals), gross necropsy (all major tissues and organs), and histology (all major tissues and organs in control and high-dose groups; gross lesions, epididymides, kidneys, lungs, testes, liver, and urinary bladders in all groups). An interim sacrifice (5 mice/sex/dose group) was performed at 30 days and blood samples were obtained for hematological and serum chemistry analysis; the remaining 10 mice/sex/dose group were examined at terminal sacrifice. The treatment had no adverse effects with respect to mortality, clinical signs, or ophthalmology. Body weight gain was slightly

(4-11%) decreased ($p < 0.05$) throughout the early part of the study in mid-dose males and high-dose males and females; at study termination, body weight gains of mid- and high-dose males and high-dose females were 97, 99, and 93%, respectively, of those of controls. Food consumption was significantly ($p < 0.05$) decreased in high-dose animals during the first week of treatment. Slight, significant ($p < 0.05$) decreases in hematocrit and erythrocytes levels were observed in high-dose females. A significant ($p < 0.05$) increase in platelet counts was observed in high-dose females at 30 days, but not at termination. Significant ($p < 0.05$) increases in serum calcium and albumin levels were observed at 30 days (in females, only albumin increased) and study termination, in high-dose males and females. At study termination, significant ($p < 0.05$) increases were observed in SGPT and alkaline phosphatase in high-dose males, and in alanine aminotransferase in high-dose females. Absolute liver weights, and liver/body weight and liver/brain weight ratios, were significantly ($p < 0.05$) increased in mid- and high-dose males and females. Gross enlargement of the liver was observed in all high-dose animals and in one mid-dose male and one mid-dose female. Brown or tan discoloration of the liver was observed in 7 of 20 high-dose animals and in one mid-dose male. Incidences of centrilobular hepatocyte hypertrophy were 3/20, 0/20, 11/20, and 20/20 for control (severity minimal), low-, mid- (minimal or slight), and high-dose groups (slight or moderate), respectively. Incidences of hyperplasia of the urinary bladder epithelium were 0/20, 1/20, 17/20, and 20/20 for control, low- (severity minimal), mid- (minimal or slight), and high-dose groups (slight or moderate), respectively. This study identifies a NOAEL of 500 ppm (96 mg/kg/day) and a LOAEL of 2000 ppm (383 mg/kg/day) for centrilobular hepatocyte hypertrophy and urinary bladder hyperplasia in mice treated in the diet for 13 weeks.

Sprague-Dawley rats (12/sex/dose group; average body weights 206-294 g) were treated by gavage with 0 or 200 mg/kg tri-n-butyl phosphate (purity 98.4%), 5 days/week, for 18 weeks (Laham et al., 1985). An additional group received similar treatment with 300 mg/kg for 6 weeks, followed by 350 mg/kg for 12 weeks. The expanded and time weighted average doses were 0, 143, and 238 mg/kg/day for the control, low-, and high-dose groups, respectively. The following parameters were used to assess toxicity: mortality, clinical signs, organ weights, body weight gain, hematology, serum chemistry, and gross necropsy and histology on 6 rats/sex/dose group. The treatment had no adverse effects with respect to clinical signs or hematology. High-dose males had significantly ($p < 0.05$) decreased body weight gain (14%) and significantly ($p < 0.05$) increased relative kidney weights. High-dose females had significantly ($p < 0.05$) decreased RBC acetylcholinesterase activity and significantly ($p < 0.05$) increased relative kidney, absolute and relative liver, and

absolute spleen weights. All low- and high-dose rats had diffuse hyperplasia of the urinary bladder epithelium and subepithelial capillaries; severity ranged from mild in females to moderate in males. Focal nodular epithelial hyperplasia was observed in urinary bladders of high-dose males (6/6) and females (1/6) and low-dose males (5/6). Slight mononuclear cell infiltration was observed in urinary bladders of one low-dose and one high-dose male. Capillary hyperplasia (1/12) and mononuclear cell infiltration (1/12) were observed in urinary bladders of control animals. No other treatment-related gross or histopathological abnormalities were observed. This study identified a LOAEL of 143 mg/kg/day for urinary bladder hyperplasia in rats treated by gavage for 18 weeks; no NOAEL was identified in this study.

Male Wistar rats (10-11/dose group; 5 weeks of age) were treated with 0, 0.5, or 1% tributyl phosphate (purity >97%) in the diet for 10 weeks (Oishi et al., 1980); using initial and final body weight and food consumption data from the study, the calculated administered doses were 0, 425, and 870 mg/kg/day. The following parameters were used to assess toxicity: body weight gain, food and water consumption, hematology, serum chemistry, organ weights (brain, liver, and kidney), and cholinesterase activity in brain, liver, and serum. Body weight gain was significantly ($p < 0.05$) decreased in the low- (17%) and high-dose (31%) groups. Food consumption was significantly ($p < 0.05$) decreased in the low- (15%) and high-dose (24%) groups. Dose-related decreases ($p < 0.05$) in absolute brain and kidney weights were observed at the low- and high-dose levels, and significantly ($p < 0.05$) increased relative brain and kidney weights were observed at these dose levels. At the low- and high-dose level, significant ($p < 0.05$) increases were observed in serum protein (high-dose only), cholesterol (high-dose only), urea nitrogen, and blood coagulation time, and significant ($p < 0.05$) decreases were observed in serum glucose levels, and in activities of serum SGOT, SGPT, and alkaline phosphatase (low-dose only). Brain cholinesterase activity was significantly ($p < 0.05$) increased in the low- and high-dose groups; with the exceptions of SGPT, alkaline phosphatase, and brain cholinesterase, the observed changes were dose-related. This study identified a LOAEL of 0.5% (425 mg/kg/day) for decreased body weight gain, and increased brain, hematological, and serum chemistry effects in rats treated in the diet for 10 weeks; no NOAEL was identified in this study.

Male Wistar rats (5 weeks of age) were treated with 0 (18 males) or 0.5% (8 males) tributyl phosphate (purity unknown) in the diet for 9 weeks (Oishi et al., 1982). Using initial and final body weight data from this study and food consumption data from a very similar study (Oishi et al., 1980), the calculated administered doses were 0 and 417 mg/kg/day. The following

parameters were used to assess toxicity: body weight gain, hematology, serum chemistry, organ weights (liver, kidney, spleen, and testes), and histology of the liver, kidney, and spleen. There was an 11% decrease in body weight gain in rats treated with tributyl phosphate, significant at $p < 0.05$; food consumption data were not reported. Relative liver, kidney, and testis weights were significantly ($p < 0.05$) increased, and absolute liver and spleen weights were significantly ($p < 0.05$) decreased in treated rats. Blood urea nitrogen levels were significantly ($p < 0.05$) increased in treated rats. No other adverse effects were observed. This study identifies a LOAEL of 0.5% (417 mg/kg/day) for decreased body and spleen weights, and increased serum BUN in rats treated in the diet for 9 weeks; no NOAEL was identified in this study.

In shorter-term studies, gross lesions of the urinary bladder were observed in male rats treated in the diet with 1500 ppm for 4 weeks (calculated dose was 129 mg/kg/day, using allometric values for body weight and food consumption from U.S. EPA, 1987) (SOCMA, 1991a); slightly decreased body weight gain was observed in male mice treated in the diet with 5000 ppm for 4 weeks (dose calculated by authors was 803 mg/kg/day) (Bio/dynamics, 1990); 20% mortality, decreased body weight gain, and renal tubular damage were observed in rats treated by gavage with 130 mg/kg/day for 1 month (Mitomo et al., 1980); degenerative changes in seminiferous tubules (1 of 4 rats), hematological and serum chemistry effects, decreased spleen weight, decreased rate of nerve conduction, and histological evidence of toxicity to the peripheral nervous system were observed in rats treated by gavage with 0.42 ml/kg/day (410 mg/kg/day) for 14 days (Laham et al., 1983, 1984).

NEUROTOXICITY

In an epidemiological study, industrial workers chronically (average length of exposure 13.3 years) exposed to aryl phosphates were evaluated for neurotoxicity (Reape, 1982). A field study, including a clinical neurological examination, measurement of nerve conduction velocity, and personal interviews, was used to assess the neurological health of the workers. In 1974, a modern hygienic system was installed in the plant to decrease exposure to airborne substances. In 1982, tributyl phosphate levels in the plant ranged from 1 to 15 ppb, depending on the work area. Other compounds present in the work areas included triaryl phosphate, dichlorobenzene, "other aryl phosphates", "other alkyl phosphates", and "other organics"; exposure to these compounds ranged from undetectable to 143 ppb. Many of the workers used in the study had worked at the plant both before and after 1974. Presumably, worker exposure to tributyl phosphate and the other compounds was much higher prior

to 1974. Observations from clinical neurological examinations, measurements of nerve conduction velocity, and personal interviews of exposed workers were not different from the normal population. The author concluded that there was no apparent association between chronic exposure of workers to low levels of aryl phosphates and development of neurological health effects.

Sprague-Dawley rats (12/sex/dose group; age 46-50 days) were treated daily by gavage with 0, 32.5, 100, or 325 mg/kg/day tributyl phosphate in corn oil, 7 days/week, for 13 weeks (Bio-Research Laboratories, 1991). The following parameters were used to assess toxicity: mortality, clinical signs, body weight gain, food consumption, motor activity tests (days 28, 62, and 92), and qualitative and quantitative functional observation battery (FOB) (1, 6, and 24 hours following first dosing, and days 7, 14, 35, 63, and 91). Gross necropsy was performed on major tissues and organs of all groups at study termination, and histopathological evaluation of neurological tissues, including brain (several areas), spinal cord (several levels), gastrocnemius muscle, and peripheral structures of the nervous system, was performed on 6 animals in each of the control and high-dose groups. Early deaths occurred in the mid- (3/24) and high-dose (7/24) groups; clinical and pathological findings indicated that some of these deaths may have resulted from aspiration of test material into the lungs. Salivation was observed postdosing in mid- (most rats; slight to moderate severity) and high-dose rats (all rats; moderate to severe). Muzzle staining and alopecia were observed in mid- and high-dose females, and muzzle staining was observed in high-dose males. Urogenital/ventral surface staining was observed in high-dose males and females. Body weight gain was significantly decreased ($p < 0.05$) in high-dose males (21%) and females (16%). Food consumption was significantly ($p < 0.05$) decreased in high-dose males during the first week of treatment. The treatment had no adverse effects with respect to qualitative and quantitative FOB assessments (grip strength and hind limb splay), motor activity tests, or gross pathology (including brain weight, length, or width). Histopathological examination of neurological tissues revealed no abnormalities. This study identified a NOAEL of 100 mg/kg/day and a LOAEL of 325 mg/kg/day for decreased body weight gain in rats treated by gavage for 13 weeks.

In a study by Laham et al. (1983), Sprague-Dawley rats (10/sex/dose group) were treated by gavage with 0, 0.28, or 0.42 ml/kg/day tributyl phosphate for 14 consecutive days; the corresponding doses were 0, 273, or 410 mg/kg/day. High-dose males had significantly ($p < 0.05$) decreased conduction velocity in the caudal nerve, and both sexes had histological evidence of toxicity to the sciatic nerve (retraction of Schwann cell processes surrounding unmyelinated fibers) at the high-dose

level. This study identified a NOAEL of 273 mg/kg/day and a LOAEL of 410 mg/kg/day for neurotoxicity in rats treated by gavage for 14 days.

In a study by Carrington et al. (1990) on White Leghorn hens, 2 oral doses of 1500 mg/kg tributyl phosphate (the oral LD50 value in hens, as determined in a preliminary trial), separated by a 21-day interval, did not produced behavioral or neuropathological evidence of delayed neurotoxicity. In the same study, a single dose of 1500 mg/kg did not inhibit brain neurotoxic esterase in hens. Johannsen et al. (1977) reported that administration of 2 oral doses of 1840 mg/kg tributyl phosphate (the oral LD50 value in hens as determined in a preliminary trial) to White Leghorn hens, separated by a 21-day interval, did not produced behavioral or neuropathological evidence of delayed neurotoxicity.

DEVELOPMENTAL TOXICITY

In a range-finding study, pregnant Sprague-Dawley rats (5 females/dose group) were treated by gavage with 0, 80, 435, 790, 1145, or 1500 mg/kg/day tributyl phosphate (purity 99.7%), in corn oil, on gestation days 6-15, then were sacrificed on gestation day 20 (Bio/dynamics Inc., 1991b). In another experiment (phase II), pregnant rats (6 females/dose group) were treated in a similar manner with 0, 600, or 790 mg/kg/day. Parameters used to assess maternal toxicity were mortality, clinical signs, body weight gain, food consumption, liver weight, and gross necropsy. Parameters used to assess developmental toxicity were pregnancy rates, early and late resorptions, and fetal viability, body weights, and external malformations; skeletal and visceral malformations were not measured. Due to the small number of animals used in the study, statistical analysis of data was not performed. The mortality rate for dams treated with 1145 or 1500 mg/kg/day was 100%; little additional data was obtained from these groups. Mortality rate was significantly ($p < 0.05$) increased in phase I dams treated with 790 mg/kg/day; however, the increased mortality rate was probably related to accidental water deprivation (this occurrence lead to the decision to perform the phase II experiment). For the purposes of this summary, results from rats treated with 790 mg/kg/day in phase II will be reported, but those from phase I will not be reported. One dam died following treatment with 790 mg/kg/day in phase II. No dams treated with <790 mg/kg/day died during the study. The physiological cause of these early deaths was not determined. Body weight gain was decreased in dams treated with 435 (gestation days 6-9), 600 (days 6-16), and 790 mg/kg/day (days 6-16). Food consumption on days 6-11 was

decreased in dams treated with 435, 600, or 790 mg/kg/day. Clinical signs (salivation, yellow A-G stains, yellow stains of ventral surface, wet yellow stains in mouth area) were observed in rats treated with dose levels of 435 mg/kg/day and higher; disorientation and poor condition were also observed in rats treated with 1145 or 1500 mg/kg/day. There was an increase in absolute and relative liver weights in rats treated with 790 mg/kg/day. Treatment with 790 mg/kg/day or lower had no adverse effects with respect to developmental toxicity.

Pregnant Sprague-Dawley rats (24 females/dose group; 64 days of age) were treated by gavage with 0, 188, 375, or 750 mg/kg/day tributyl phosphate (purity 100%), in corn oil, on gestation days 6-15, then were sacrificed on gestation day 20 (Bio/dynamics, 1991c). Parameters used to assess maternal toxicity were mortality, clinical signs, body weight gain, food consumption, liver weight, and gross necropsy. Parameters measured to assess developmental toxicity were pregnancy rates, early and late resorptions, and fetal viability, body weights, and external, visceral, and skeletal variations and malformations. High-dose dams had a significant ($p < 0.05$) increase in mortality rate (7/24); six of the seven deaths were considered to be related to treatment, although the physiological cause of these deaths was not reported. A dose-related decrease in maternal body weight gain was observed during gestation days 6-16, significant ($p < 0.05$) in low- (5%), mid- (6%), and high-dose (16%) dams. Food consumption on gestation days 6-11 was significantly ($p < 0.05$) decreased in mid- (12%) and high-dose (37%) dams. A dose-related increase in clinical signs (salivation, yellow staining of the skin, red A-G stains, wetness of ventral abdominal area, excessive lacrimation) was observed in low-, mid, and high-dose dams. A dose-related increase in relative liver weights was observed, significant ($p < 0.05$) in all treatment groups; this effect was probably related to the observed decrease in body weight gain, rather than a treatment-related effect. No abnormalities were observed following gross necropsy of dams. The treatment had no adverse effects with respect to pregnancy rate, number of corpora lutea, implantations, or early or late resorptions, or fetal viability, sex ratio, external or visceral abnormalities, or skeletal malformations. Fetal weight was significantly ($p < 0.05$) decreased at the high-dose level. The number of fetuses with one or more ossification variations was significantly ($p < 0.05$) increased in all treatment groups; these developmental delays were considered to be mild in the low- and mid-dose groups (some were in the range of historical controls), but were extensive in the high-dose group. This study identified a LOAEL of 188 mg/kg/day for slight maternal and developmental toxicity and a FEL of 750 mg/kg/day for maternal mortality; no NOAELs were identified in this study.

In a range-finding study, pregnant New Zealand White rabbits (5 females/dose group) were treated by gavage with 0, 50, 250, 412, 775, 1137, or 1500 mg/kg/day tributyl phosphate (purity 99.7%), in corn-oil, on gestation days 6-18, then were sacrificed on gestation day 30 (Bio/dynamics Inc., 1991d). Parameters used to assess maternal toxicity were mortality, clinical signs, body weight gain, food consumption, liver weight, and gross necropsy. Parameters measured to assess developmental toxicity were pregnancy rates, early and late resorptions, and fetal viability, body weights, and external malformations; skeletal and visceral malformations were not measured. Due to the small number of animals used in the study, statistical analysis of data was not performed. Mortality rate was 100% for does treated with 775, 1137, or 1500 mg/kg/day, and 20% for does treated with 250 or 412 mg/kg/day; the physiological cause of these early deaths was not determined. No further data were obtained from groups treated with 775 mg/kg/day or higher. Body weight gain was decreased at 412 mg/kg/day, but not at lower treatment levels. The treatment had no clear adverse effects with respect to food consumption. Incidence of resorptions were slightly increased at 50, 250, and 412 mg/kg/day; however, this effect was not dose-related. Other parameters of developmental toxicity were not adversely affected at 50, 250, or 412 mg/kg/day.

Pregnant New Zealand White rabbits (18 females/dose group) were treated by gavage with 0, 50, 150, or 400 mg/kg/day tributyl phosphate (purity 99.7%), in corn oil, on gestation days 6-18, then were sacrificed on gestation day 30 (Bio/dynamics Inc., 1991e). Parameters measured to assess maternal toxicity were mortality, clinical signs, body weight gain, food consumption, liver weights, gross necropsy, and histology of gross abnormalities. Parameters measured to assess developmental toxicity were pregnancy rates, early and late resorptions, fetal viability, body weights, and external, visceral, and skeletal variations and malformations. The treatment had no adverse effects with respect to clinical signs, relative liver weights, pregnancy rates, abortion, premature delivery, pre-implantation loss, or fetal viability, body weights, sex distribution, or external, visceral, or skeletal abnormalities. Two high-dose females died, one from handling errors and one from unknown causes. Body weight gain on gestation days 6-9 was 15, -9, -15, and -34 g in control, low-, mid- and high-dose (significant at $p < 0.05$) does, respectively. Non-significant ($p > 0.05$) decreases in food consumption (9-21%) from day 7-14 of gestation, and increases in number of resorptions/female and ratio of resorptions/implants were observed in high-dose does. The authors considered these statistically non-significant changes to be suggestive of a treatment-related effect in high-dose does. This study identifies a NOAEL of 150 mg/kg/day and a LOAEL of 400 mg/kg/day for slight maternal toxicity, and a NOAEL of 400

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mg/kg/day for developmental toxicity in rabbits; no LOAEL for developmental toxicity was identified in this study.

REPRODUCTIVE TOXICITY

In a one-generation range-finding study, Sprague-Dawley rats (10/sex/dose group) were treated in the diet with 0, 100, 300, 1500, or 5000 ppm tributyl phosphate during 2-week pre-mating and breeding periods (SOCMA, 1991a); using allometric values for body weight and food consumption (U.S. EPA, 1987), the calculated doses were 0, 9, 26, 129, or 431 mg/kg/day for male rats and 0, 10, 29, 147, or 490 mg/kg/day for female rats. Male rats were sacrificed following breeding, and gross necropsy was performed. Female rats received additional treatment during gestation, lactation, and weaning, then were sacrificed on postnatal day 21 for gross necropsy. Thus, males and females received approximately 4 and 10 weeks of treatment, respectively. F1 generation pups were culled to 5/sex/litter/dose group at postnatal day 4, and were sacrificed on postnatal day 21 for histological examination of urinary bladders of both sexes and testes of males. Gross necropsy of adults revealed changes in the urinary bladder (thickening, hyperemia, and soft, velvety texture) in males treated with 1500 ppm and both sexes treated with 5000 ppm. One male weanling in the 1500 ppm group and 2 male and 2 female weanlings in the 5000 ppm groups died prior to scheduled sacrifice. Hyperplasia of the urinary bladder epithelium was observed in 1/10, 0/10, 0/10, 7/10, and 8/8 female weanlings, and 0/10, 1/10, 1/10, 1/9, and 7/8 male weanlings, in the 0, 100, 300, 1500, and 5000 ppm groups, respectively; these incidences were significantly ($p < 0.05$) higher in female weanlings at 1500 and 5000 ppm, and males weanlings at 5000 ppm. The severity of hyperplasia was dose-related and ranged from minimal to moderate. Because testicular lesions were observed in only one high-dose male pup, the authors concluded that "no unequivocal treatment-related lesions" were observed in the testes of male weanlings. No further information regarding experimental method or results was described in this preliminary report. This study identified a NOAEL of 300 ppm (26-29 mg/kg/day) and a LOAEL of 1500 ppm (129-147 mg/kg/day) for urinary bladder effects in female weanling and adult male rats.

DERIVATION OF THE CHRONIC RfD

Evidence of slight neurotoxicity was observed in rats treated by gavage with 410 mg/kg/day tributyl phosphate for 14 days (Laham et al., 1983). However, in a more comprehensive 13-week gavage study in rats, no neurotoxicity was observed at dose levels up to 325 mg/kg/day (Bio-Research Laboratories, 1991). In addition, no neurotoxicity was evident in workers exposed for

many years to 1-15 ppb tributyl phosphate and other aryl phosphates (Reape, 1982). No evidence for delayed neurotoxicity was observed in hens exposed orally to 1500-1840 mg/kg, over a 21-day period (Johannsen et al., 1977; Carrington et al., 1990). Thus, it appears unlikely that long-term exposure to tributyl phosphate would produce neurotoxicity.

Slight developmental toxicity was observed in rats at 188 mg/kg/day (Bio/dynamics, 1991c); no NOAEL was identified for this study. Because this was the only oral developmental toxicity study located for rats, a NOAEL for developmental toxicity could not be identified in rats. However, the developmental effects observed at 188 mg/kg/day were minimal (some were within the range of historical controls; Bio/dynamics, 1991c), indicating that the NOAEL for developmental toxicity in rats may fall at or near 188 mg/kg/day. In a range-finding study, no apparent developmental effects were observed at dose levels of 790 mg/kg/day and lower (Bio/dynamics, 1991b). A free-standing NOAEL of 400 mg/kg/day was identified for developmental toxicity in rabbits (Bio/dynamics, 1991e).

Urinary bladder hyperplasia was observed in male rats exposed in the diet to 1000 ppm (68 mg/kg/day) tributyl phosphate and in female rats exposed to 5000 ppm (423 mg/kg/day) (FMC, 1985); in rats of both sexes treated by gavage with 143 mg/kg/day (Laham et al., 1985); in female and male weanling rats exposed to 1500 ppm (147 mg/kg/day) and 5000 ppm (490 mg/kg/day), respectively, in utero and during lactation (SOCMA, 1991a); and in mice of both sexes exposed to 2000 ppm (383-462 mg/kg/day) (Bio/dynamics Inc., 1991a). In addition, gross lesions of the urinary bladder were observed in male rats exposed to 1500 ppm (129 mg/kg/day) tributyl phosphate in the diet, and in female rats exposed to 5000 ppm (490 mg/kg/day) (SOCMA, 1991a). The urinary bladder hyperplasia observed at 1000 ppm in male rats (FMC, 1985) represented the lowest LOAEL (68 mg/kg/day) for any adverse effect observed in the reviewed studies. Thus, urinary bladder hyperplasia was identified as the critical effect, and the NOAEL of 200 ppm (14 mg/kg/day) from the FMC (1985) study was used to derive the chronic RfD. An uncertainty factor of 3000 was used for intra- (10) and interspecies (10) variation, the use of a subchronic study (10), and for limitations in the database (3, no chronic or multigeneration reproduction studies). A provisional chronic RfD of 5E-3 mg/kg/day was derived by dividing the rat NOAEL of 14 mg/kg/day by the uncertainty factor of 3000.

Confidence in the principle study is high. This is an adequate subchronic oral toxicity study using an acceptable number of animals of both sexes and a large range of dose levels, measuring a sufficient number of endpoints, and identifying both

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a NOAEL and LOAEL. Confidence in the data base is low. Although several subchronic studies identified urinary bladder hyperplasia as the critical-effect, no oral studies of chronic duration were located. No NOAEL was identified for developmental toxicity in rats, although a LOAEL was identified at a dose level producing minimal effects (Bio/dynamics, 1991c). Reproductive effects were observed in weanling rats in a preliminary one-generation study (SOCMA, 1991a); however, no 2-generation reproductive toxicity studies were located. Reflecting low confidence in the data base, confidence in the chronic RfD is low.

CARCINOGENICITY

A carcinogenicity study is currently being performed by FMC Corporation (SOCMA, 1991b). In this study, rats (50/sex/dose group) are being treated in the diet with 0, 200, 700, or 3000 ppm tributyl phosphate for 24 months. As of 10/09/91, one mid-dose and one high-dose rat had died. Following gross necropsy, several large (0.1-0.6 mm diameter) calculi were observed in the urinary bladders of each of these rats. Urinary bladder calculi had not been previously reported in rats administered tributyl phosphate. This information was reported in response to the TCSA Section 8(e) ruling of Notice of Substantial Risk. No further information is available regarding experimental method or results in this preliminary report.

GENOTOXICITY

Tributyl phosphate was negative for genotoxicity in the following studies: a mutagenicity assay with the TA98, TA100, TA1535, TA1537, and TA1538 strains of *Salmonella typhimurium*, both with and without metabolic activation (Microbiological Associates, 1977); a mutagenicity assay with the TA98, TA100, TA1535, and TA1537 strains of *Salmonella typhimurium*, both with and without metabolic activation (Bayer, 1985); a CHO/HGPRT mutation assay, both with and without metabolic activation (Microbiological Associates, 1990a); a cytogenetics assay with Chinese Hamster ovary cells, both with and without metabolic activation (Microbiological Associates, 1990b); an in vivo cytogenetics bone marrow assay in rats (Microbiological Associates, 1990c); a mutagenicity assay with the hisC117, hisG46, hisD3052, TA1530, TA1531, TA1532, and TA1534 strains of *Salmonella typhimurium*, a mutagenicity assay with WP2 isogenic strains of *Escherichia coli*, and a recessive lethal mutation test in the Oregon-R strain of *Drosophila melanogaster* (Hanna and Dyer, 1975). Positive results for genotoxicity were apparently observed at 500 ug/plate in a Russian study on mutagenicity in the TA1535 and TA1538 strains of *Salmonella typhimurium* (Gafieva and Chudin, 1986, as cited in RTECS, 1992).

WEIGHT-OF-EVIDENCE CLASSIFICATION

There are no data evaluating carcinogenicity of tributyl phosphate in humans or animals. In addition, the vast majority of in vitro and in vivo tests indicate that tributyl phosphate is negative for genotoxicity. According to the guidelines for evaluating the weight-of-evidence of human carcinogenic potential (U.S. EPA, 1986), tributyl phosphate is placed in Group D, not classifiable as to carcinogenicity in humans.

DERIVATION OF ORAL SLOPE FACTOR

The U.S. EPA (1986) guidelines state that slope factors are not derived for weight-of-evidence Group D chemicals; therefore, no attempt was made to derive an oral slope factor for tributyl phosphate.

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Attachment 4

**Risk Assessment Issue Paper for:
Subchronic Inhalation Toxicity For Mixed Xylenes CASRN 1330-20-7**

INTRODUCTION

Review documents available for xylenes are a Drinking Water Criteria Document (U.S. EPA, 1985), a Health and Environmental Effects Profile (U.S. EPA, 1986), a Health Effects Assessment Document (U.S. EPA, 1989), and an ATSDR toxicological profile (ATSDR, 1990). These documents were examined for information pertinent to derivation of a subchronic RfC. The following computer searches for xylenes were conducted and screened: TOXLINE (1990-93), HSDB, and RTECS.

Commercial-grade (mixed) xylene (CAS No. 1330-20-7) is composed of approximately 20% o-xylene, 40% m-xylene, and 20% p-xylene, with about 15% ethylbenzene and smaller amounts of other aromatic hydrocarbons (IARC, 1989). Most studies in experimental animals and in human volunteers have examined the effects of either single xylene isomers or xylene mixtures with varying ethylbenzene concentrations (up to 40%). In this memorandum, the term xylene will refer to any mixture of isomers.

The following guidelines and regulations are available for xylene. OSHA lists an 8-hour TWA of 100 ppm (434 mg/m³) and a 15-min STEL of 150 ppm (651 mg/m³) (OSHA, 1992). ACGIH lists a TLV TWA of 100 ppm (434 mg/m³) and a STEL of 150 ppm (651 mg/m³) (ACGIH, 1991, 1992). These values are intended to protect workers from sensory irritation and central nervous system effects of xylene. NIOSH (1992) lists a REL TWA of 100 ppm (434 mg/m³) and 150 ppm (651 mg/m³) as a 10-min ceiling. The U.S. EPA (1993) verified an oral RfD of 2 mg/kg/day for xylene. The RfD is based on a NOAEL of 250 mg/kg/day for hyperactivity and decreased body weight and increased mortality.

The U.S. EPA RfD/RfC Work Group reviewed the data base on the toxicity of inhaled xylene and determined that there are insufficient data to derive a chronic RfC. The status of the RfC is Not Verifiable (U.S. EPA, 1992). No studies in humans were located regarding the effects of subchronic or chronic exposure to xylene. In addition, subchronic and less than subchronic exposure studies in animals were considered inadequate because the respiratory tract was not examined and/or neurotoxicity was not assessed. Also, a route-to-route extrapolation of data from

oral studies was not recommended because xylenes have been shown to cause respiratory tract irritation in humans.

A review of the up-to-date literature searches listed above did not reveal any additional or more recent information that could be used for derivation of a subchronic RfC for xylene. Thus, a subchronic RfC for xylene can not be derived at this time.

INHALATION TOXICITY

Derivation of an inhalation RfC for mixed xylenes is not recommended because data regarding the toxicity of inhaled mixed xylenes are not suitable for risk assessment. No studies in humans were located regarding the effects of repeated acute, subchronic, or chronic exposure to mixed xylenes. There are earlier reports of occupational exposure to xylenes, however, many of these reports involved exposure to mixed aromatic hydrocarbons (NIOSH, 1975). There are no reports of subchronic or chronic exposure of humans to individual xylene isomers. However, there are numerous reports of effects in humans following acute exposure to m- or p-xylene; neurotoxicity and eye, nose, and throat irritation have been observed in subjects exposed to approximately 100 ppm for 5 days (U.S. EPA, 1989). Similar effects have been observed in humans exposed to mixed xylenes (Gamberale et al., 1978; Carpenter et al., 1975). Because these studies involved single exposures for 70 minutes or less, they are not suitable for the derivation of a chronic RfC. Two subchronic (Carpenter et al., 1975; Savolainen et al., 1979) and 2 less than subchronic animal studies (Pryor et al., 1987; Leong et al., 1984) involving inhalation exposure to mixed xylenes were identified. These four studies did not adequately examine the respiratory tract and/or assess for neurotoxicity, and therefore are not adequate for the derivation of an RfC for mixed xylenes. Because exposure to xylene can result in respiratory tract irritation in humans, a route-to-route extrapolation of data from the NTP (1986) gavage study is not recommended.

Gamberale et al. (1978) exposed 15 male subjects (aged 21-33 years) at rest to mixed xylenes (12.1% o-xylene, 54.4% m-xylene, 12.8% p-xylene, and 20.7% ethylbenzene) at concentrations of 0, 435 and 1300 mg/cu.m for 70 minutes. The xylene and air (control condition) were supplied via a breathing valve. The subjects were divided into three groups, all subjects were exposed to each concentration level with a day between exposures. The order of the exposure levels varied between the groups. In a second study, 8 of the previously exposed men were exposed to 1300 mg/cu.m for 70 minutes. The subjects exercised (100 W) for the first 30 minutes of the exposure period. In both experiments,

five neurological performance tests (reaction time addition, sample and choice reaction times, short-term memory, and critical flicker fusion frequency) were administered prior to xylene exposure and during the last 35 minutes of exposure. The subjects completed a questionnaire on subjective reactions to the exposure. The majority of the subjects did not report subjective symptoms (sickness, headache, intoxication). However, a relationship between exposure levels and frequency of subjective symptoms was observed (data not presented). The authors noted that there was a slight tendency among the subjects to shift their responses closer to the extremes "drowsy", "distracted", and "lazy" after xylene exposure. No effects on the performance tests were noted in the first experiment. In the second experiment, decreased performance on all five tests ($p < 0.05$) was observed. The difference in the results of the two studies is probably the result of exercise-induced increased uptake of xylenes at the 1300 mg/cu.m exposure level. In the first experiment, the mean xylene uptake following exposure to 1300 mg/cu.m was 541 mg. When the subjects exercised for 30 minutes (second experiment), the mean xylene uptake after 70 minutes of exposure to 1300 mg/cu.m was 1210 mg.

Carpenter et al. (1975) exposed groups of 6-7 volunteers (aged 21-60 years, sex not reported) to 110, 230, 460 and 690 ppm (478, 999, 1997, 2996 mg/cu.m) mixed xylenes (7.6% o-, 65.0% m-, 7.8% p-xylene, 19.3% ethylbenzene) for 15 minutes. The subjects were exposed to only one concentration a day, in the following order 230, 110, 460, then 690 ppm. All subjects were able to detect the presence of xylene in the air. Exposure to 460 and 690 ppm resulted in an increased incidence of eye irritation as compared to the two lower concentrations (0/6, 1/7, 4/6, 4/6, respectively). One subject reported dizziness or lightheadedness with a slight loss of balance during exposure to 690 ppm. Three other subjects reported mild dizziness without a loss of balance during exposure to 690 ppm. The incidence of dizziness at the other 3 exposure levels were 0/6, 1/7, 0/6, respectively. Throat irritation was reported in 1/6, 0/7, 1/6, and 2/6 subjects exposed to 110, 230, 460, 690 ppm, respectively. No other exposure related changes were reported. In a separate experiment, Carpenter et al. (1975) estimated that the odor threshold for mixed xylenes was between 0.14 and 1.4 ppm.

Groups of 25 male Harlan-Wistar rats and 4 male beagle dogs were exposed to 0, 180, 460 or 810 ppm (0, 781, 1997 or 3517 mg/cu.m) mixed xylenes (7.6% o-, 65.0% m-, 7.8% p-xylene, 19.3% ethylbenzene) 6 hours/day, 5 days/week for 13 weeks (Carpenter et al., 1975). Groups of 3 rats were killed after 3 and 7 weeks of exposure. The following parameters were used to assess toxicity: body weight, liver and kidney weights, hematology (cell counts, hemoglobin, hematocrit), clinical chemistry (BUN, SGOT, SGPT,

serum alkaline phosphatase), and histopathology of major organs and tissues including lung, trachea, liver, kidney and nasal mucosa (dogs only). No consistent alterations were observed in any of these parameters for either species.

Lione (1981) examined the histopathology slides from the Carpenter et al. (1975) study. After 7 weeks of exposure, the incidence of minimal regenerative epithelium (data not shown) in the kidney was greater in rats exposed to 810 ppm. At the 13-week sacrifice, minimal regenerative epithelium was also seen in the rats exposed to 460 ppm. However, both Carpenter et al. (1975) and Lione (1981) stated that no clear cut treatment related differences in the incidence of severity of regenerative epithelium and tubular dilatations from that seen in controls were observed. No histopathologic alterations were observed in the kidneys of dogs.

Groups of 20 male Wistar rats were exposed to 0 or 300 ppm (0 or 1303 mg/cu.m) mixed xylenes (85% m-xylene, and 15% o- and p-xylene) 6 hours/day, 5 days/week for 5-18 weeks (Savolainen et al., 1979). No effect on body weight gain or cerebral protein or RNA content were observed. A significant ($p < 0.05$) decrease in microsomal superoxide dismutase activity was observed after 5 weeks of exposure, by 18 weeks of exposure there was a significant ($p < 0.05$) increase in enzyme activity. Behavioral effects of xylene exposure were assessed using an open-field test. Altered preening was observed after 9 and 12 weeks of exposure. No other behavioral effects were observed.

Leong et al. (1984) exposed groups of male Sherman rats (sample size not reported) to 690 ppm mixed xylenes (o-, m-, p-xylene, with m-xylene predominating) 6 hours/day, 5 days/week for 6 weeks. The test atmosphere consisted of xylene vapors and fine aerosols (arithmetic mean 0.6; geometric mean 0.5). During exposure the animals appeared lethargic and crouched together motionless. It is not known if this was the result of the irritative properties of xylene or was a neurotoxic effect. The only histopathologic alterations (trachea, lungs, liver, kidneys, adrenals, stomach, colon, urinary bladder, and gonads examined) that were observed were pulmonary lesions attributable to chronic murine pneumonia. No effect on hematologic parameters (hemoglobin, hematocrit, cell counts), mortality, body weight gain, or organ weights were observed. Deficiencies of this study include not reporting the sample size, the nasal cavity was not examined, and neurotoxicity was not adequately assessed.

Groups of 12 male weanling Fischer 344 rats were exposed to 0, 800, 1000 or 1200 ppm (0, 3474, 4342, 5210 mg/cu.m) mixed xylenes (10% o-, 80% m-, and 10% p-xylene) 14 hour/day 7 days/week for 6 weeks (Pryor et al., 1987). Two days after the

termination of exposure, the rats were trained to perform a multisensory conditioned avoidance response (CAR) task. Brainstem auditory-evoked response (BAER) thresholds were measured 2 weeks after exposure termination. Exposure to 1200 ppm resulted in slight impairment in acquisition of the 4 kHz tone CAR. No effect on nonaversive shock or light CARs were found. Behavioral auditory thresholds and BAER thresholds were elevated at all three exposure levels. A relationship between the frequencies at which there was hearing loss and xylene concentration was observed. In the 1200 ppm group, hearing loss was observed at 4 kHz or greater. Whereas, hearing loss was observed at 12 and 20 kHz in the rats exposed to 800 ppm. A LOAEL of 800 ppm was identified; this is 8-fold higher than the LOAEL for neurotoxic effects in humans exposed to p-xylene for 5 days (Hake et al., 1981).

In another experiment, Pryor et al. (1987) exposed groups of 12 male rats to 1700 ppm (7381 mg/cu. m) mixed xylenes for 4 hours or to 1450 ppm (6296 mg/cu.m) for 8 hours/day for 3 days. Hearing loss was not observed in the rats exposed to 1700 ppm for 4 hours. A slight to moderate effect was observed after 8 hours of exposure to 1450 ppm xylenes. After 3 days of exposure to 1450 ppm, a marked effect on hearing was observed.

Groups of male and female Sprague-Dawley rats (10-60/sex/group) were exposed to 0, 60, 250 or 500 ppm (262, 1085 or 2171 mg/cu.m) technical grade mixed xylenes (composition not specified) for 6 hour/day 7 days/week during a 130-day pre-mating period and a 20-day mating period (Bio/dynamics, 1982). Pregnant females were also exposed on gestational day 1-20 and lactational days 5-20. There were 3 groups of rats exposed to 500 ppm: xylene exposed females mated with exposed males; exposed females mated with unexposed males; and unexposed females mated with exposed males. On day 4 of lactation, pups were removed from their litter and pooled with all other pups in the same treatment group. Pups were then randomly distributed among the dams. Pups were weighed and examined externally on days 1, 4 and 21 of lactation. Histopathology was completed on the major organs and tissues from pups killed on day 21 of lactation. A decrease ($p < 0.05$) in the female mating index was observed in the 250 ppm and 500 ppm females mated with unexposed males. Lower mating indices were not observed in the females exposed to 500 ppm and mated with exposed males. The authors noted that the decrease in the mating index may be attributed to the unusually high mating indices (100%) in the control group. No effect on mating indices was observed in the males. Although no effect on pup body weight was observed at birth, a significant decrease ($p < 0.05$) in body weight was observed on day 4, 14 (no statistically significant) and 21 of lactation was observed in the offspring of females exposed to 500 ppm and mated with exposed males. In pups killed

21 day post-weanling; decreases in absolute ($p < 0.05$) and relative (not significant) ovary weights were observed at the 250 and 500 ppm (exposed females mated with exposed males). This was not observed in pups killed 49 days post-weanling. No effect on testis weight was observed. Twenty control dams and 12 dams exposed to 500 ppm and mated with exposed males were killed on gestational day 21. No exposure related effects on the incidence of external, soft tissue, or skeletal malformations were observed in the fetuses. The incidence of fetuses with at least one ossification variation was slightly but statistically higher at the 500 ppm level as compared to controls. No other effects were observed in the F0 or F1 generations. This study identified a NOAEL of 250 ppm and LOAEL of 500 ppm for developmental toxicity. The NOEL for reproductive effects is 500 ppm.

In an abstract, Hass and Jakobsen (1987) reported the results of a study in which groups of 36 pregnant rats were exposed to 0 or 200 ppm (0 or 868 mg/cu.m) 6 hours/day on gestational days 4-20. No signs of maternal toxicity were observed. Small increases in the mean number of resorptions and in the incidence of fetuses with retarded ossification of the skull were found (the authors did not report whether this was statistically significant). A nonsignificant decrease in rotorod performance was observed in the offspring of exposed dams. No effects on fetal body weight or the incidence of soft-tissue or skeletal malformations were observed.

Groups of 20 pregnant CFY rats were exposed to 1000 mg/cu.m mixed xylenes (10% o-, 50% m-, 20% p-xylene and 20% ethylbenzene) continuously during gestational days 9-14 (Hudak and Ungvary, 1978). The rats were killed on day 21 of gestation. No effect on maternal weight gain, litter size, fetal weight, or the incidence of external, internal, or skeletal malformations were observed. Significant ($p < 0.05$) increases in the incidence of fused sternbrae or extra ribs were observed. Poor reporting of the methods and results preclude defining a NOAEL/LOAEL value.

Ungvary and Tatrai (1985) exposed groups of pregnant CFLP mice and New Zealand rabbits to mixed xylenes (composition not specified). Groups of rats were also exposed to xylene; however, the authors did not state if the rats were exposed to mixed xylenes or to a single isomer. Mice (15 dams/group) were exposed to 0, 500 or 1000 mg/cu.m xylenes 3-4 hours/day on days 6-15 of gestation, and killed on gestational day 18. No information on maternal toxicity was reported. The incidences of weight retardation and skeletal retardation were significantly ($p < 0.05$) increased in the offspring of mice exposed to 1000 mg/cu.m. Rabbits (10 does/group) were continuously exposed on gestational days 7-20 to 0, 500 or 1000 mg/cu.m, and killed on gestational day 30. No effect on maternal weight gain was observed.

Increased relative liver weight was observed in the does exposed at the highest concentration. Decreased body weight was observed in the female offspring of rabbits exposed to 500 mg/cu.m. At the 1000 mg/cu. m exposure level, 3/10 does died, 6/10 aborted, and in 1/10 there was total resorption. In the controls these effects were not observed. The authors did not report the cause of death in the does. NOAELs and LOAELs can not be identified from this study because of the inadequate reporting of the methods and results.

Moser et al. (1985) exposed groups of male CD-1 mice to reagent grade xylenes (mixture of o-, m- and p-xylene and ethylbenzene, not specified) for 30 minutes. The mice were exposed to concentrations ranging from 500-7000 ppm (2171-30,393 mg/cu.m). Operant behavior was used to assess toxicity. An increase in the rate of operant responding was observed at exposure levels ranging from 1400-4000 ppm (6079-17,368 mg/cu.m). Suppression of responding was observed at 7000 ppm. Gross ataxia and prostration were also observed at the 7000 ppm exposure level.

A depression on the reinforcement rate in an operant schedule (fixed ratio) was observed in 5 male Fischer 344 rats exposed to 113.8, 212.0 and 445.8 ppm xylene (494.1, 920.5 or 1935.6 mg/cu.m) (mixture of o-, m- and p-xylene and ethylbenzene, not specified) for 2 hours (Ghosh et al., 1987). Rats were exposed to each concentration with a day between concentrations. The effect was observed during the first hour of exposure, acute tolerance appeared to develop during the second hour of exposure. No effect on reinforcement rate was observed in 4 rats exposed to 98 ppm (425 mg/cu.m) for 5 hours.

NTP (1986) administered by gavage technical grade xylenes (9% o-, 60% m-, 14% p-xylene, 17% ethylbenzene) to groups male and female (50/sex/species/group) F344/N rats and B6C3F1 mice 5 days/week for 103 weeks. A corn oil vehicle was used. Rats were treated with 0, 250 or 500 mg/kg and the mice with 0, 500 or 1000 mg/kg. In the high-dose male rats, a decrease ($p < 0.05$) in survival was observed. When the incidence of accidental deaths (3/50 and 11/50 for 0 and 500 mg/kg groups, respectively) were factored out, the difference in survival was no longer statistically significant (Fisher Exact Test). No other differences in survival were observed. No compound related effects on the incidence of histopathologic alterations (all major tissues and organs examined) were observed. Hyperactivity was observed in all high-dose mice 5-30 minutes after dosing. This effect was observed consistently between weeks 4 and 103. No effect on survival or the incidence of nonneoplastic lesions (major tissues and organs examined) were observed in the mice.

NTP (1986) also conducted a 13-week gavage study in rats and mice. Male and female rats (10/sex/group) were treated by gavage with 0, 62.5, 125, 250, 500 or 1000 mg/kg mixed xylenes 5 days/week for 13 weeks. In the high-dose males, a decrease (15%) in body weight gain relative to controls was observed. No histopathologic alterations were observed. Groups 10 male and 10 female mice were dosed by gavage with 0, 125, 250, 500, 1000 or 2000 mg/kg mixed xylenes 5 days/week for 13 weeks. In the high-dose animals, weakness, lethargy, short and shallow breathing, unsteadiness, tremors, and paresis were observed after dosing and lasted 15-60 minutes. Two female mice in the 200 mg/kg group died before the terminal sacrifice. The authors noted that gavage errors could not be discounted. Body weight gain in the high-dose females was 17% less than the controls. Histopathologic examination of the major tissues and organs did reveal any compound related effects.

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Attachment 5

Oral and Dermal Absorption Information

(10/09/92)

Acetone

U.S. EPA documents (1984, 1988) did not review data regarding dermal absorption of acetone. ATSDR (1992) included discussion of data from humans and animals showing that acetone is absorbed through the skin, but absorption efficiencies were not measured. It is possible to make a rough estimate of dermal absorption factor based on analogy to benzene. Studies of dermal absorption of benzene in humans and animals have shown that this compound is almost completely (99%) absorbed across the skin when covered with a watch glass to prevent volatilization, but that absorption falls to trivial levels (<0.2% in all species tested, 0.05% in humans) when application is to the skin uncovered, due to volatilization (Franz, 1984; Skowronski et al., 1988). Acetone (vapor pressure = 231.1 mm Hg at 25°C) is even more volatile than benzene (vapor pressure = 95.2 mm Hg at 25°C), so the dermal absorption fraction for acetone is expected to be similarly small. Therefore, the value of 0.05% determined experimentally for benzene in humans is recommended to replace the "proposed" value of 3% for acetone.

Available documents from U.S. EPA (1984, 1988) and ATSDR (1992) review data showing that 74-83% of acetone was detected in expired air following oral administration to rats. The upper range of the experimentally determined value, 83%, is recommended to replace the "proposed" value of 100%.

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(9/23/91)

Anthracene

Human data regarding carcinogenic or noncarcinogenic effects following exposure to anthracene via inhalation, oral or dermal routes are restricted to a report associating gastrointestinal toxic effects in humans who consumed anthracene-containing laxatives for prolonged periods of time. Hematological effects have been associated with intravenous exposure of cancer patients to anthracene-containing chemotherapeutic agents, but the data are inconclusive because of concomitant exposure to other agents and the lack of control groups. Anthracene is a component of mixtures (e.g., tobacco smoke, coal tar, soots and coke oven emissions) that have been associated with human cancer, but animal testing (see next paragraph) has not produced carcinogenic effects with exposure to anthracene.

Limited animal testing has not identified adverse health effects following oral exposure to anthracene. Toxic effects were not observed in a subchronic gavage study with mice and a chronic dietary study with rats. Parenteral exposure studies identified hepatic effects in acutely exposed rats, but no developmental effects in offspring exposed in utero. Data regarding carcinogenic or noncarcinogenic effects in animals following single or repeated inhalation exposure to anthracene are not available. Carcinogenic effects have not been observed in animals following chronic oral exposures, lung-implant exposure or dermal exposure (including tests for tumor promotion on mouse skin). Reports of noncarcinogenic effects in animals following dermal exposure were not available.

U.S. EPA (1993) has verified an oral RfD for anthracene based on no observable effects in a subchronic gavage study with mice.

Based on no available human data and inadequate animal data, anthracene has been classified as a Group D carcinogen - not classifiable as to carcinogenicity (U.S. EPA, 1993).

The available data provide no indication that anthracene absorbed dermally will produce effects not observed with oral exposure; therefore, oral-to-dermal extrapolation appears appropriate.

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(10/09/92)

Arsenic

Available OHEA documents on arsenic (U.S. EPA, 1980, 1984a) and the ATSDR (1989) Toxicological Profile on Arsenic did not review quantitative data for the dermal absorption of arsenic. However, according to ATSDR (1991) Toxicological Profile on Arsenic no quantitative studies were located on absorption of inorganic arsenic in humans after dermal exposure. Uptake of arsenic into blood or tissues was undetectable for up to 24 hours in rats whose tails were immersed in solution of sodium arsenate for 1 hour. However, arsenic began to increase in blood, liver and spleen over the next 5 days (Dutkiewicz, 1977). The rate of uptake was estimated to be 1-33 $\mu\text{g}/\text{cm}^2/\text{hr}$. These findings suggest that dermal exposure leads initially to arsenic binding to skin and that the bound arsenic may slowly be taken up into the blood, even after exposure ends. The U.S. EPA Office of Pesticide Programs (U.S. EPA, 1984b) recommended the use of a value of 0.1% for dermal absorption of inorganic arsenic compounds from arsenic-laden wood dusts, based on a report that the upper limit was 0.1% for dermal absorption of arsenic (as sodium arsenate in aqueous solutions) in rats (Dutkiewicz, 1977). In the absence of direct information on dermal absorption efficiencies of arsenic in soil, the value of 0.1% is recommended to replace the "proposed value" of 1%.

Available EPA documents (U.S. EPA, 1980, 1984a) and the ATSDR Toxicological Profile on Arsenic reviewed data for humans indicating that greater than 95% of ingested, water-soluble arsenic is absorbed by the gastrointestinal tract; data for animals indicate that poorly soluble arsenic compounds are absorbed less efficiently. These data indicate that the assumption of a value of 95% for oral absorption of inorganic arsenic compounds is reasonable; this value is identical to the "proposed value" of 0.95.

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(10/09/92)

Barium

Data for the dermal absorption of barium were not reviewed in available EPA documents on barium (U.S. EPA, 1984; 1985; 1989). (There is no ATSDR document on barium.) Shah and Guthrie (1986) cited results from experiments by Wahlberg showing that

solutions of metallic salts, including CrCl_3 , Na_2CrO_4 , CoCl_2 , ZnCl_2 , CdCl_2 , and HgCl_2 applied to the skin of guinea pigs, displayed absorption efficiencies less than 2%. In general, inorganic cations such as barium would be expected to display an affinity to bind to soil particles, thereby diminishing their bioavailability. Thus, in the absence of human or animal data for dermal absorption of barium in soil, the "proposed value" of 1% seems reasonable to use in estimating absorbed doses from dermal exposure to barium in soil.

Available EPA documents on barium (U.S. EPA, 1984; 1985; 1989) did not review human data on the absorption efficiency for orally administered barium. However a published study has reported that greater than 91% of barium in dietary components is absorbed by humans. Lisk et al. (1988) observed that only 0.81% and 9.09% of a dose of barium from Brazil nuts were excreted in the urine and feces by an individual during six days following ingestion, thereby indicating that 90.9 to 100% of the barium had been absorbed and 90.1% remained in the body. The ingested Brazil nuts contained 179 mg Ba (1953 ug Ba/g Brazil nuts x 91.76 g Brazil nuts = 179 mg Ba).

Animal studies reviewed in available EPA documents on barium (U.S. EPA, 1984; 1985; 1989) indicate that absorption efficiencies of orally administered barium are dependent upon age of the animals, the accompanying anion and the dosage level applied. McCauley and Washington (1983) reported that the relative absorption rates of barium salts in drinking water followed the order of chloride > sulfate > carbonate, but did not provide quantitative data on absorption efficiencies. Cuddihy and Ozog (1973) reported that hamsters given a single intragastric tracer dose of radiolabeled BaCl_2 only absorbed 11% of the dose within a 4-hour period, but cautioned that intestinal absorption may not have been completed in 4 hours. Taylor et al. (1962) reported that young rats given single oral doses of barium displayed higher absorption efficiencies (85%) than those of adult rats (10%). Clary and Tardiff (1974) examined absorption efficiencies of BaCl_2 in male weanling rats given single oral doses ranging from 1 to 125 mg/kg and reported that total uptake of barium increased with increasing dosage, but relative uptake (i.e., absorption efficiency) decreased with increasing dosage. In general, the data for animals with orally administered barium salts in aqueous solution provide estimates that range from 10% to 85%.

It is unknown if the apparent discrepancy between the lower estimates in the animal studies and the 91% value for humans reported by Lisk et al. (1988) is due to differences in absorption between species, differences in bioavailability

between forms of barium (e.g., in food versus drinking water) or some other factor. The oral absorption efficiency value of 91% is recommended for use in adjusting the oral RfD for barium to an absorbed-dose basis. This judgement is based on the view that the oral RfD is for protection of humans and is best adjusted to an absorbed-dose basis using human absorption efficiency data. The basis for the "proposed value" of 1% was not provided in the Dirk's Farm document.

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(2/09/93)

Benz[a]anthracene

(ATSDR, 1990; IARC, 1973; U.S. EPA, 1990; 1993)

Human data regarding carcinogenic or noncarcinogenic effects associated with inhalation, oral or dermal exposure to benz[a]anthracene alone were not available. Benz[a]anthracene is a component of complex mixtures that have been associated with human cancer. These mixtures include tobacco smoke, coal tar and coke oven emissions.

Increased incidences of pulmonary tumors and liver tumors have been reported for mice given repeated gavage or intraperitoneal administrations of benz[a]anthracene. Benz[a]anthracene produced skin tumors in mouse skin-painting assays for complete carcinogenicity and tumor initiating activity. Subcutaneous injection of benz[a]anthracene into mice produced injection site tumors.

Benz[a]anthracene is classified to be a Group B2 carcinogen - Probable Human Carcinogen based on inadequate evidence in humans and sufficient evidence for carcinogenicity from animal tests (U.S. EPA, 1993).

Oral-to-dermal extrapolation is not appropriate for benz[a]anthracene because of the evidence that dermal exposure to benz[a]anthracene causes skin cancer and the uncertainty that the oral slope factor will protect against the local carcinogenic effect of dermally applied benz[a]anthracene.

Benzo[a]pyrene

Human data regarding carcinogenic or noncarcinogenic effects associated with inhalation, oral or dermal exposure to benzo[a]pyrene alone were not available. Benzo[a]pyrene is a component of complex mixtures, including tobacco smoke, coal tar and coke oven emissions, that have been associated with human cancer.

Benzo[a]pyrene produced skin tumors when applied dermally to mice, rats and rabbits. Local tumors have been observed in mice, rats, guinea pigs, monkeys and hamsters following subcutaneous or intramuscular administration of benzo[a]pyrene. Respiratory tract tumors were produced in hamsters following intratracheal instillations of benzo[a]pyrene. Oral administration of benzo[a]pyrene resulted in stomach tumors in rats and hamsters, and inhalation exposure produced respiratory tumors in hamsters.

Benzo[a]pyrene is a Group B2 carcinogen - Probable Human Carcinogen based on inadequate evidence in humans and sufficient evidence for carcinogenicity in animal assays (U.S. EPA, 1993).

Oral-to-dermal extrapolation is not appropriate for benzo[a]pyrene because of the evidence that dermal exposure to benzo[a]pyrene causes skin cancer and the uncertainty that the oral slope factor will protect against the local carcinogenic effect of dermally applied benzo[a]pyrene.

REFERENCES FOR BENZO[a]PYRENE:

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

U.S. EPA. 1993. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Toxicological Profile for Polycyclic Aromatic Hydrocarbons. U.S. Public Health Service. Atlanta, GA. Public Comment Draft.

IARC (International Agency for Research on Cancer). 1983. Polynuclear aromatic compounds, Part 1, Chemical, Environmental and Experimental Data. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 32. WHO, IARC, Lyon, France.

IARC (International Agency for Research on Cancer). 1973. Certain polycyclic aromatic hydrocarbons and heterocyclic compounds. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man, Volume 3. WHO, IARC, Lyon, France.

(2/11/92)

Benzo[b]fluoranthene

Human data regarding carcinogenic or noncarcinogenic effects associated with inhalation, oral or dermal exposure to benzo[b]fluoranthene alone were not available. Benzo[b]fluoranthene is a component of complex mixtures, including tobacco smoke, coal tar and coke oven emissions, that have been associated with human cancer.

Sufficient evidence for the carcinogenicity of benzo[b]fluoranthene is available from animal testing. Increased tumor incidences at the injection site and at distant sites have been observed in mice following intraperitoneal injections of benzo[b]fluoranthene. Increased incidences of lung tumors occurred in rats given lung implants containing benzo[b]fluoranthene. Benzo[b]fluoranthene produced skin tumors when applied dermally to mice.

Benzo[b]fluoranthene is a Group B2 carcinogen - Probable Human Carcinogen based on inadequate evidence in humans and sufficient evidence for carcinogenicity in animal assays (U.S. EPA, 1993).

Oral-to-dermal extrapolation is not appropriate for benzo[b]fluoranthene because of the evidence that dermal exposure to benzo[b]fluoranthene causes skin cancer and the uncertainty that the oral slope factor will protect against the local carcinogenic effect of dermally applied benzo[b]fluoranthene.

REFERENCES FOR BENZO[b]FLUORANTHENE:

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

U.S. EPA. 1993. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Toxicological Profile for Polycyclic Aromatic Hydrocarbons. U.S. Public Health Service. Atlanta, GA.

(10/09/92)

Beryllium

Data regarding dermal absorption of beryllium were reviewed by U.S. EPA (1987b), ATSDR (1988) and ATSDR (1991). According to ATSDR (1991), skin ulceration in workers exposed to beryllium occurred only after the skin was abraded (Williams, et. al., 1987). It is unlikely that beryllium is absorbed through intact skin. An experiment in rats showed that small amounts of beryllium can be absorbed through the tail, but did not determine an absorption factor. Because of the chemical properties of beryllium, it is unlikely that significant amounts could be absorbed through the

skin. Dermal absorption values for other metallic salts (CrCl_3 , Na_2CrO_4 , CoCl_2 , ZnCl_2 , CdCl_2 , HgCl_2) in guinea pigs were all less than 2% (Shah and Guthrie, 1986). These values would be expected to be even lower following exposure to the compound in soil due to adsorption of the cations to soil particles. Therefore, the "proposed" dermal absorption factor of 1% appears to be reasonable for beryllium.

U.S. EPA (1980, 1987a, 1987b) and ATSDR (1988) reviewed the available data regarding absorption of beryllium from the gastrointestinal tract. No data were available for humans. However, based on studies in animals, oral absorption of beryllium in humans is expected to be very limited. Experiments in animals suggest that <1% of ingested beryllium is absorbed through the gut, with the more soluble salts, such as beryllium sulfate, being absorbed better than insoluble salts, such as beryllium oxide. In one study, low absorption of beryllium sulfate was attributed to formation of phosphate precipitate in the intestine. The authors of this study surmised that absorption of beryllium occurred predominantly in the stomach. Because absorption from the stomach would be expected to depend on gastric emptying time, which can vary widely, this finding suggests that beryllium absorption might be subject to large variations. However, such variations are not seen in the existing data. The "proposed" oral absorption factor of 1% appears to be reasonable, given the existing data.

REFERENCES FOR BERYLLIUM

ATSDR (Agency for Toxic Substances and Disease Registry). 1988. Toxicological Profile for Beryllium. ATSDR, U.S. Public Health Service, Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry). 1991. Toxicological Profile for Beryllium. Public Comment Draft. ATSDR, U.S. Public Health Service, Atlanta, GA.

Shah, P.V. and F.E. Guthrie. 1986. Dermal and gastrointestinal absorption of environmental contaminants. In: Reviews in Environmental Toxicology 2. E. Hodgson, Ed. Elsevier, N.Y.

U.S. EPA. 1980. Ambient Water Quality Criteria Document for Beryllium. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80/024. PB81-117350.

U.S. EPA. 1987a. Health Effects Assessment for Beryllium and Compounds. Prepared by the Office of Health and Environmental

Assessment, Environmental Criteria and Assessment Office,
Cincinnati, OH. for the Office of Emergency and Remedial
Response, Washington, D.C. EPA 600/8-88/020. PB88-179460.

U.S. EPA. 1987b. Health Assessment Document for Beryllium.
Office of Health and Environmental Assessment, Environmental
Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-
84/026F. PB88-179205.

Williams WJ, Williams WR, Kelland D, et al. 1987. Beryllium
skin disease. Proc. 11th World Conference Sarcoidosis, Milan
1987. Elsevier Press.

(12/29/92)

Bis(2-ethylhexyl)phthalate
(ATSDR, 1989, 1991; U.S. EPA, 1991, 1992)

Data regarding carcinogenic or noncarcinogenic effects in
humans following inhalation, oral or dermal exposure to bis(2-
ethylhexyl)phthalate [also known as di(2-ethylhexyl)phthalate]
were not available in OHEA or ATSDR review documents on this
compound. Animals orally exposed to bis(2-ethylhexyl)phthalate
have shown carcinogenic and noncarcinogenic effects on the liver,
adverse effects on the testes and reproductive performance, and
adverse effects on fetal development. Bis(2-ethylhexyl)phthalate
did not produce genotoxic effects in multiple bacterial and
animal assays.

The U.S. EPA (1992) classified bis(2-ethylhexyl)phthalate as
a Group B2 compound - Probable Human Carcinogen based on
inadequate human data and sufficient evidence that liver tumor
responses occur in rats and mice of both sexes. An oral slope
factor of $1.4E-2$ per (mg/kg)/day was derived. The U.S. EPA
(1992) verified an RfD of $2E-2$ mg/kg/day for systemic toxicity
from bis(2-ethylhexyl)phthalate based on a LOAEL of 19 mg/kg/day
for increased relative liver weight in a guinea pig sub-chronic-
to-chronic oral study.

Dermal toxicity data for bis(2-ethylhexyl)phthalate were not
located in OHEA and ATSDR review documents on this compound.
There is no evidence that dermal exposure to bis(2-
ethylhexyl)phthalate will produce effects different from those
produced by oral exposure; therefore oral-to-dermal extrapolation
is appropriate.

REFERENCES

ATSDR. 1989. Toxicological Profile for Di(2-ethylhexyl)phthalate. Agency for Toxic Substances and Disease Registry. U.S. Public Health Service. Atlanta, GA.

ATSDR. 1991 Toxicological Profile for Di(2-ethylhexyl)phthalate. Agency for Toxic Substances and Disease Registry. U.S. Public Health Service. Atlanta, GA. Public Comment Draft.

U.S. EPA. 1991. Drinking Water Criteria Document for Phthalic Acid Esters (PAES). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-D009.

U.S. EPA. 1992. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

(2/24/92)

BIS(2-ETHYLHEXYL)PHTHALATE

ENSR assumed a dermal absorption efficiency value of 0.4% for BEHP from soil, based upon a report that 0.4% of an occluded dermal dose of radiolabeled BEHP (dissolved in ethanol) was recovered in the urine and feces after 24 hours in rats (El Sisi et al., 1989). ENSR noted that dermal absorption of BEHP in soil is likely to be less than that under the conditions of the El Sisi et al. experiment, because of the adsorption of BEHP to soil particles. However, ENSR also noted that the use of the 0.4% value would be protectively conservative. The value of 0.4% does not account for the percentage of the dose that may have been absorbed and not excreted; however, El Sisi et al. (1989) reported that, 7 days after application, most (98%) of the applied dose remained at the skin area of application or was adsorbed onto the plastic cap used for occluding the dose, thereby supporting the contention that very little of the BEHP was absorbed by the skin.

ENSR's use of 0.4% for dermal absorption of BEHP in soil appears to be justified by the El Sisi et al. data and to be consistent with RAGS HHEM Part A guidelines (U.S. EPA, 1989). Data for dermal absorption of BEHP other than that presented by El Sisi et al. (1989) were not located by the ATSDR (1989,1991). The Drinking Water Criteria Document on Phthalic Acid Esters

(U.S. EPA, 1991) did not review data on dermal absorption of BEHP.

REFERENCES FOR BEHP

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Di (2-ethylhexyl) phthalate. ATSDR, U.S. Public Health Service, Atlanta, GA. NTIS PB/90/194484/AS

ATSDR (Agency for Toxic Substances and Disease Registry). 1991. Toxicological Profile for Di (2-ethylhexyl) phthalate. Public Comment Draft. ATSDR, U.S. Public Health Service, Atlanta, GA. NTIS PB/90/194484/AS

El Sisi, A.E., D.E. Carter and I.G. Sipes. 1989. Dermal absorption of phthalate diesters in rats. Fund. Appl. Toxicol. 12: 70-77.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Volume 1. Human Health Evaluation Manual (Part A). Prepared by the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-89/002.

(10/09/92)

2-Butanone

As reviewed by the ATSDR (1991), data regarding the fractional absorption of dermally applied 2-butanone are not available. No discussion of dermal absorption is contained in U.S. EPA documents on 2-butanone (U.S. EPA, 1984; 1985; 1989). The dermal absorption of 2-butanone (applied either as a neat compound or contained in soil) is likely to be much less than 100% due to volatilization of the compound from the skin. 2-Butanone displays a vapor pressure of 98.0 mm Hg at 25 C which is comparable to that of benzene (95.2 mm Hg at 25 C). The dermal absorption of undiluted benzene by humans was severely limited by volatilization (see benzene entry in this document). In the absence of any quantitative data on the fractional dermal absorption of 2-butanone in humans or animals, the recommended value for benzene, 0.05%, is recommended for 2-butanone based on the similarity of the vapor pressures of the two compounds. The basis of the "proposed value" of 0.03 was not provided in the Dirk's Farm document.

Data regarding the fractional absorption of orally administered 2-butanone in humans or animals were not available in Agency documents (U.S. EPA, 1984; 1985; 1989) or in the ATSDR (1991) Toxicological Profile for 2-butanone. The "proposed value" of 0.95 is consistent with demonstrated oral fractional

absorption for certain other volatile organic chemicals (see benzene entry in this document) and is recommended for the adjustment of oral toxicity values to an absorbed dose basis.

REFERENCES FOR 2-BUTANONE

ATSDR. 1991. Toxicological Profile for 2-Butanone. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. Draft for Public Comment.

U.S. EPA. 1984. Health Effects Assessment for Methyl Ethyl Ketone. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Emergency and Remedial Response, Office of Solid Waste and Emergency Response, Washington, DC. EPA/540/1-86-003.

U.S. EPA. 1985. Health and Environmental Effects Profile for Methyl Ethyl Ketone. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response.

U.S. EPA. 1989. Updated Health Effects Assessment for Methyl Ethyl Ketone. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. ECAO-CIN-H003a.

(2/24/92)

CADMIUM

ENSR used a value of 0.1% for dermal absorption of cadmium in soil. This value appears to be reasonable based on data reviewed in the Drinking Water Criteria Document for Cadmium (U.S. EPA, 1989). 1.8% of dermal doses of cadmium (as CdCl_2 in a 0.239 M aqueous solution) was absorbed by guinea pigs in a 5-hour period; at lower concentrations less than 1% was absorbed (Skog and Wahlberg, 1964). Due to cadmium adsorption to soil particles, dermal absorption is expected to be considerably less from soil than under the conditions of the Skog and Wahlberg experiment. The ATSDR (1989,1991) Toxicological Profile on Cadmium did not cite specific values for dermal absorption efficiencies for cadmium.

REFERENCES FOR CADMIUM

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Cadmium. ATSDR, U.S. Public Health Service, Atlanta, GA. NTIS PB/89/194476/AS

ATSDR (Agency for Toxic Substances and Disease Registry). 1991. Toxicological Profile for Cadmium. Public Comment Draft. ATSDR, U.S. Public Health Service, Atlanta, GA. NTIS PB/89/194476/AS

Skog, E. and J.E. Wahlberg. 1964. A comparative investigation of the percutaneous absorption of metal compounds in the guinea pig by means of radioactive isotopes: ^{51}Cr , ^{58}Co , ^{65}Zn , $^{110\text{m}}\text{Ag}$, $^{115\text{m}}\text{Cd}$, ^{203}Hg . J. Invest. Derm. 43: 187-197. Cited in U.S. EPA, 1986

U.S. EPA. 1989. Drinking Water Criteria Document for Cadmium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. NTIS PB89-192140

U.S. EPA. 1993. Integrated Risk Information System (IRIS). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

(2/06/92)

Dermal Absorption of Cadmium

Wester et al. (1991) studied the percutaneous absorption of cadmium chloride from soil. Following is the presentation of the experimental results of this study as well as the recommended absorption percentage for use in exposure assessments.

Experimental Results

Wester et al. (1991) studied the percutaneous absorption of cadmium chloride from water and soil. Radioactive cadmium-109 was mixed with soil (Yolo County 65-California-57-8) and applied to human cadaver skin mounted in glass diffusion cells with human plasma as the receptor fluid. Two soil application rates were used -- 20 mg/cm² and 40 mg/cm². The soil was removed from the skin samples with soap and water after 16 hours of exposure. The average percentages of cadmium absorbed by samples from 2 human skin sources (3 samples from each source) were 0.08% (0.02% in the receptor fluid and 0.06% in skin) and 0.2% (0.07% in receptor fluid and 0.13% in skin) when soil was applied at 40 mg/cm². The average percentages absorbed from a soil application of 20 mg/cm²

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were 1.0% (0.02% in the receptor fluid and 0.08% in the skin) for each of the two sources. The average absorption from all twelve samples was 0.1%.

Analysis of Data

There was no difference in percentages of cadmium absorbed from soil applications of 20 and 40 mg/cm². To account for uncertainty which may arise from different soil types, soil loading, concentrations, and other conditions, a range of 0.1% to 1.0% is recommended for use in exposure assessments.

Reference

Wester, R.C., Maibach, H.I., Sedik, L., Melendres, J., Dizio, S., Jamall, I. and Wade, M. 1991. In vitro percutaneous absorption of cadmium from water and soil. Toxicol. Abstracts of the 30th Annual Meeting 11: 289.

(2/24/92)

CADMIUM

ENSR used oral absorption efficiency values for cadmium of 5% from drinking water and 2.5% from food, which are consistent with previous Agency actions on cadmium. These values were used in a toxicokinetic model by the U.S. EPA to derive oral RfDs for cadmium in drinking water and for cadmium in food (U.S. EPA, 1992).

ENSR used a value of 0.1% for dermal absorption of cadmium in soil. This value appears to be reasonable based on data reviewed in the Drinking Water Criteria Document for Cadmium (U.S. EPA, 1989). 1.8% of dermal doses of cadmium (as CdCl₂ in a 0.239 M aqueous solution) was absorbed by guinea pigs in a 5-hour period; at lower concentrations less than 1% was absorbed (Skog and Wahlberg, 1964). Due to cadmium adsorption to soil particles, dermal absorption is expected to be considerably less from soil than under the conditions of the Skog and Wahlberg experiment. The ATSDR (1989) Toxicological Profile on Cadmium did not cite specific values for dermal absorption efficiencies for cadmium.

REFERENCES FOR CADMIUM

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Cadmium. ATSDR, U.S. Public Health Service, Atlanta, GA. NTIS PB/89/194476/AS

Skog, E. and J.E. Wahlberg. 1964. A comparative investigation of the percutaneous absorption of metal compounds in the guinea pig by means of radioactive isotopes: ⁵¹Cr, ⁵⁸Co, ⁶⁵Zn, ^{110m}Ag, ^{115m}Cd, ²⁰³Hg. J. Invest. Derm. 43: 187-197. Cited in U.S. EPA, 1986

U.S. EPA. 1989. Drinking Water Criteria Document for Cadmium. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. NTIS PB89-192140

U.S. EPA. 1992. Integrated Risk Information System (IRIS). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

(5/7/91)

CARBON TETRACHLORIDE (CASRN 56-23-5)

U.S. EPA 1989: Human: No pertinent studies located. However, it would be anticipated that it is well absorbed from the GI tract of humans since it is readily absorbed from the GI tract of animals. Animals: Readily absorbed.

ATSDR 1989: Human: No studies located. However, it is anticipated that it is well absorbed from the GI tract in humans since it is readily absorbed from the GI tracts in animals.

REFERENCES FOR CARBON TETRACHLORIDE:

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Carbon Tetrachloride. ATSDR, U.S. Public Health Service. Draft for Public Comment.

U.S. EPA. 1989. Updated Health Effects Assessment for Carbon Tetrachloride. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

(2/91)

Oral Absorption Factor for Chloroform (CASRN 67-66-5)

Updated HEA 1988:

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Humans: nearly complete. Mice, rats and Monkeys: 93-98%.

HAD 1985: Animals: virtually completely absorbed. Rats, mice, monkeys 93-98% recovery of radioactivity in exhaled air, urine and carcass.

AWQCD 1980:

Animals: Approximately 100%

ATSDR 1991 Public Comment Draft:

Humans: ~100% absorbed rapidly.

Animals: 93-98% absorption.

REFERENCES:

ATSDR. 1991. Toxicological Profile for Chloroform. Agency for Toxic Substances and Disease Registry. U.S. Public Health Service. Atlanta, GA. Public Comment Draft.

U.S. EPA. 1980. Ambient Water Quality Criteria for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC.

U.S. EPA. 1985. Health Assessment Document for Chloroform. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for Office of Air Quality Planning and Standards, Washington, DC.

U.S. EPA. 1988. Updated Health Effects Assessment for Chloroform. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

(2/11/92)

Chrysene

(ATSDR, 1990; U.S. EPA, 1990; 1992)

Human data regarding carcinogenic or noncarcinogenic effects following inhalation, oral or dermal exposure were not available. However, chrysene is a known component of mixtures (e.g. tobacco smoke, coal tar, soots and coke oven emissions) that have been associated with human cancer.

Animal studies examining noncarcinogenic effects following oral, dermal or inhalation exposure to chrysene are not available.

Chrysene produced carcinomas and malignant lymphomas in mice after intraperitoneal injection and skin carcinomas in mice following dermal exposure.

Neither the HEAST (U.S. EPA, 1991) nor IRIS (U.S. EPA, 1992) lists an oral RfD or an inhalation RfC for chrysene. The U.S. EPA (1990) determined that data were insufficient for derivation of a long-term Drinking Water HA for chrysene.

Chrysene is classified to be a Group B2 carcinogen - probable human carcinogen based on the availability of no human data and sufficient data from animal tests (U.S. EPA, 1992).

Oral-to-dermal extrapolation is not appropriate for chrysene because of the evidence that dermal exposure to chrysene causes skin cancer and the uncertainty that the oral slope factor will protect against the local carcinogenic effect of dermally applied chrysene.

REFERENCES

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

U.S. EPA. 1992. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Toxicological Profile for Polycyclic Aromatic Hydrocarbons. U.S. Public Health Service. Atlanta, GA. Public Comment Draft.

(6/05/92)

COPPER

ENSR assumed a value of 0.1% for dermal absorption of copper from soil; this value was recommended by the Massachusetts Department of Environmental Quality Engineering (DEQE, 1989) as a default value for dermal absorption of inorganic compounds from soil. The ATSDR (1990) identified no data on the rate or extent of dermal absorption of copper in humans or animals. The U.S. EPA (1987) cited studies that reported that copper can permeate human skin and that 3.3% of copper applied to the skin of cats as a radiolabeled saline solution of a copper complex (bis[glycinato]copper[II]) penetrated the skin within 24 hours (Walker et al., 1977). Other data regarding the fractional dermal absorption of copper were not available. ENSR's assumption of 0.1% dermal absorption of copper from soil appears reasonable; copper ions would be expected to bind to anionic clay particles and organic matter in soil, thereby competing with, and limiting, absorption by the skin.

REFERENCES FOR COPPER

ATSDR. 1990. Toxicological Profile for Copper. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

DEQE (Massachusetts Department of Environmental Quality Engineering). 1989. Guidance for Disposal Site Risk Characterization and Related Phase II Activities. In Support of the Massachusetts Contingency Plan. Office of Research and Standards. Report # 70.

U.S. EPA. 1987. Drinking Water Criteria Document for Copper. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH. for the Office of Drinking Water, Washington, DC. February, 1987.

Walker, W.R., R.R. Reeves, M. Brosnan and G.D. Coleman. 1977. Profusion of intact skin by a saline solution of bis(glycinato) copper (II). Bioinorganic Chem. 7: 271. Cited in U.S. EPA, 1987.

(6/24/92)

COPPER

ENSR assumed that no absorption adjustments were necessary for the three oral exposure scenarios for copper (i.e., the AAFs are equal to 1). ENSR stated that the "oral dose-response value for copper ($3.7\text{E-}2$ mg/kg/day)... is based on a oral study with copper sulfate in humans". There are no oral toxicity values for copper listed on IRIS (U.S. EPA, 1992a); the HEAST (U.S. EPA, 1992b) lists the drinking water standard (MCL) of 1.3 mg/L in the columns for subchronic and chronic RfD, with the explanation that the drinking water criteria document (U.S. EPA, 1987) concluded that toxicity data were inadequate for calculation of an RfD for copper. The most recent list of U.S. EPA (1991a) drinking water regulations and health advisories lists no HAS or DWELs for copper, but lists 1.3 mg/L as the MCLG and MCL for copper. In a Final Rule on drinking water regulations for lead and copper, the Agency stated that the basis for the MCLG for copper was a LOAEL for gastrointestinal disturbances of 5.3 mg/day ($7.6\text{E-}2$ mg/kg/day for a 70-kg person) from human clinical case studies. An uncertainty factor of two was applied and standard daily consumption of 2 liters of water per day was assumed (U.S. EPA, 1991b).

ENSR used a value of 60% for the oral absorption efficiency of copper in humans from the diet, based upon a report by Weber et al. (1969). As reviewed by the U.S. EPA (1984; 1987) and the ATSDR (1990), the Weber et al. (1969) study provided single oral doses of radioactive copper as copper acetate to human patients and observed a range of absorption efficiencies (15-97%, with an average of approximately 60%). Studies in animals have indicated that the absorption of copper from the gastrointestinal tract is influenced by many factors including competition with other metals, the amount of copper in the stomach, the presence of certain dietary components (e.g., dietary ascorbate, phytates and fiber can interfere with absorption, presumably through complexing), and the form of copper ingested (ATSDR, 1990). The value of 60% oral absorption of copper appears to be a conservative general estimate for humans based on the available data.

ENSR assumed a value of 0.1% for dermal absorption of copper from soil; this value was recommended by the Massachusetts Department of Environmental Quality Engineering (DEQE, 1989) as a default value for dermal absorption of inorganic compounds from soil. The ATSDR (1990) identified no data on the rate or extent of dermal absorption of copper in humans or animals. The U.S. EPA (1987) cited studies that reported that copper can permeate human skin and that 3.3% of copper applied to the skin of cats as a radiolabeled saline solution of a copper complex (bis[glycinato]copper[II]) penetrated the skin within 24 hours (Walker et al., 1977). Other data regarding the fractional dermal absorption of copper were not available. ENSR's assumption of 0.1% dermal absorption of copper from soil appears reasonable; copper ions would be expected to bind to anionic clay particles and organic matter in soil, thereby competing with, and limiting, absorption by the skin.

REFERENCES FOR COPPER

ATSDR. 1990. Toxicological Profile for Copper. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

DEQE (Massachusetts Department of Environmental Quality Engineering). 1989. Guidance for Disposal Site Risk Characterization and Related Phase II Activities. In Support of the Massachusetts Contingency Plan. Office of Research and Standards. Report # 70.

U.S. EPA. 1984. Health Effects Assessment for Copper. Prepared by Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH. for the Office of

Emergency and Remedial Response. Revised Final Draft. ECAO-CIN-HO25.

U.S. EPA. 1987. Drinking Water Criteria Document for Copper. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH. for the Office of Drinking Water, Washington, DC. February, 1987.

U.S. EPA. 1991a. Drinking Water Regulations and Health Advisories. Office of Drinking Water. Washington, DC.

U.S. EPA. 1991b. Maximum Contaminant Level Goals and National Primary Drinking Water Regulations for Lead and Copper; Final Rule. Federal Register 56 (110): 26460-26564.

U.S. EPA. 1992a. Integrated Risk Information System (IRIS). Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH.

U.S. EPA. 1992b. Health Effects Summary Tables. Annual FY 1992. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH.

Walker, W.R., R.R. Reeves, M. Brosnan and G.D. Coleman. 1977. Profusion of intact skin by a saline solution of bis(glycinato) copper (II). Bioinorganic Chem. 7: 271. Cited in U.S. EPA, 1987.

Weber, P.M., S. O'Reilly, M. Pollycove and L. Shipley. 1969. Gastrointestinal absorption of copper: Studies with ⁶⁴Cu, ⁶⁵Zn, a whole body counter and the scintillation camera. J. Nucl. Med. 10: 591. Cited in U.S. EPA, 1987.

(6/3/91)

Dermal Absorption of Cyanide (CASRN 57-12-5)

Ingestion of high doses of cyanide can rapidly cause death by producing histotoxic hypoxia. Lower doses of cyanide can be effectively detoxified by rhodanese in the liver. The nervous system and the thyroid appear to be the target organs for the toxicity of oral cyanide exposure. U.S. EPA (1993) derived a verified oral RfD for free cyanide based on weight loss, thyroid effects and nervous system effects in chronically exposed rats. Cyanide has not been shown to be carcinogenic following any route of exposure.

Dermal exposure to cyanide has resulted in neurological effects in both humans and animals. In the human studies, however, concomittent inhalation and oral exposure occurred. Doses associated with the neurological effects have not been quantitated.

Ingested cyanide is effectively detoxified by the liver, but it is uncertain if dermally applied cyanide would be detoxified as effectively. It seems possible that dermally absorbed cyanide (due to the lack of a "first pass effect") may be subject to a more widespread distribution throughout the body before being detoxified in the liver. Therefore, performing an oral-to-dermal extrapolation would not be appropriate because of the uncertainty that the oral RfD for cyanide would provide protection for the effects caused by dermal exposure.

References:

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Cyanide. ATSDR, U.S. Public Health Service. Atlanta, GA.

ATSDR (Agency for Toxic Substances and Disease Registry). 1991. Toxicological Profile for Cyanide. ATSDR, U.S. Public Health Service. Atlanta, GA. Draft for Public Comment.

U.S. EPA. 1988a. Drinking Water Criteria Document for Cyanide. Prepared by the Office of Health and Environmental Assessment,

(2/06/92)

DDT

Wester et al. (1990) studied percutaneous absorption of DDT *in vitro* in human skin and *in vivo* in rhesus monkeys. Following is a description of the experimental protocols used in this study and presentation of the results. Also, an analysis of the results is provided as they apply to assessment of exposure to chemicals in the environment.

Experimental Results

Wester et al. (1990) studied the percutaneous absorption of DDT applied in soil and acetone *in vitro* using human skin and *in vivo* in rhesus monkeys. Soil composed of 26% sand, 26% clay, and 48% silt, containing 10 ppm ¹⁴C-labeled DDT was applied to human skin samples with surface areas of 1 cm². The soil application

rate was 40 mg/cm². After 24 hours, the surface of the sample was washed with soap and water. The investigators found that the DDT tended to bind to the skin rather than enter the human plasma receptor phase. After 24 hours, an average of 95.6% of the topically applied radioactivity was found in the surface wash, 1% was in the skin sample, and 0.04% was in the receptor fluid. For 6 samples from 2 donors, the percentages of the applied dose found in the skin after 24 hours ranged from 0.3 to 1.8%. For the same dose of DDT applied in acetone, an average of 63.7% was in the surface wash, 18.1% was in the skin sample, and 0.08% was in the receptor fluid 24 hours after application. The percentage of the DDT applied in acetone that was bound to the skin after 24 hours differed substantially between the 2 donors. The 3 samples from the first donor contained 7.9%, 5.0%, and 7.1% of the applied dose after the surface wash. The samples from the second donor contained 25.9%, 25.1%, and 37.8% of the applied dose.

Wester et al. (1990) also measured *in vivo* percutaneous absorption in rhesus monkeys. The percentage of topically applied DDT absorbed over a 24-hour exposure period averaged 3.3%. Percentages of applied dose of DDT absorbed for three subjects were 2.7%, 3.4%, and 3.7%. When 4 monkeys received the same dose topically applied in acetone, the average percent absorbed was 18.9% and the percents absorbed for each subject were 9.2%, 30.5%, 13.8%, and 22.2%.

Analysis of Data

In the *in vivo* experiment using human skin, 1% of the applied dose of DDT was found in the skin after 24 hours and 0.04% was found in the receptor fluid, for a total of 1.04% of the applied dose absorbed over 24 hours from an application of 40 mg soil/cm². In rhesus monkeys, the average percentage of DDT absorbed from a soil loading of 40 mg/cm² with a concentration of 10 ppm DDT was 3.3%.

The amount of soil applied by Wester et al. (1990), 40 mg/cm², is large compared to the soil adherence values of 0.2 to 1.0 mg/cm², which are believed to be typical for environmental exposures. The extent to which these differences affect the percent of the applied dose that could be expected to be absorbed is unclear.

An upper bound on absorption might be set by observing that the maximum percentage of applied dose of DDT absorbed was 37.8% in human skin samples and 30.5% in rhesus monkey samples. However, because of the wide range of absorption fractions predicted by the data, no attempt has been made to recommend a

range of values for the percutaneous absorption of DDT. Further research is required on the effect of soil loading on the percentage of DDT absorbed.

Reference

Wester, R.C., Maibach, H.I., Bucks, D.A.W., Sedik, L., Melendres, J., Liao, C., and Dizio, S. 1990. Percutaneous absorption of [¹⁴C]DDT and [¹⁴C]benzo[a]pyrene from soil. *Fundamental and Applied Toxicology* 15: 510-516.

(12/29/92)

Dibenzo[a,h] anthracene

Human data regarding carcinogenic or noncarcinogenic effects associated with inhalation, oral or dermal exposure to dibenzo[a,h]anthracene alone were not available. Dibenzo[a,h]anthracene is a component of complex mixtures, including tobacco smoke, coal tar and coke oven emissions, that have been associated with human cancer.

Oral exposure to dibenzo[a,h]anthracene has been associated with the development of tumors in mice. Tumors in mice also have been observed following pulmonary implantation, intratracheal instillation, intravenous injection and dermal application of dibenzo[a,h]anthracene. Injection-site tumors following intramuscular or subcutaneous injection have been observed in several species including mice, rats and guinea pigs. Dibenzo[a,h]anthracene has produced genotoxic effects in several assay systems.

Dibenzo[a,h]anthracene is a Group B2 compound - Probable Human Carcinogen based on inadequate evidence in humans and sufficient evidence for carcinogenicity in animal assays (U.S. EPA, 1993).

Oral-to-dermal extrapolation is not appropriate for dibenzo[a,h]anthracene because of the evidence that dermal exposure causes skin cancer and the uncertainty that the oral slope factor will protect against the local carcinogenic effect of dermally applied dibenzo[a,h]anthracene. RAGS HHEM Part 1 (page 7-16) (U.S. EPA, 1989) provides guidance to support this recommendation in the statement that "it is inappropriate to use the oral slope factor to evaluate the risks associated with dermal exposure to carcinogens such as benz[a]pyrene (sic) which cause skin cancer through a direct action at the point of application". Dibenzo[a,h]anthracene and other PAHs are expected

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to cause skin cancer through a mechanism similar to the mechanism through which benzo[a]pyrene acts.

REFERENCES FOR DIBENZO[a,h]ANTHRACENE:

ATSDR. 1990. Toxicological Profile for Polycyclic Aromatic Hydrocarbons. Agency for Toxic Substances and Disease Registry. U.S. Public Health Service. Atlanta, GA.

IARC (International Agency for Research on Cancer). 1973. Certain polycyclic aromatic hydrocarbons and heterocyclic compounds. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. WHO, IARC, Lyon, France. Volume 3.

IARC (International Agency for Research on Cancer). 1983. Polynuclear aromatic compounds, Part 1, Chemical, Environmental and Experimental Data. In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. Volume 32.

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

U.S. EPA. 1993. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

(2/11/92)

Indeno[1,2,3-cd]pyrene

Human data regarding carcinogenic or noncarcinogenic effects associated with inhalation, oral or dermal exposure to indeno[1,2,3-cd]pyrene alone were not available. Indeno[1,2,3-cd]pyrene is a component of complex mixtures, including tobacco smoke, coal tar and coke oven emissions, that have been associated with human cancer.

Sufficient evidence for the carcinogenicity of indeno[1,2,3-cd]pyrene is available from animal testing. Increased tumor incidences at the injection site have been observed in mice following subcutaneous injections of indeno[1,2,3-cd]pyrene. Increased incidences of lung tumors occurred in rats given lung implants containing indeno[1,2,3-cd]pyrene. Indeno[1,2,3-

cd]pyrene also produced skin tumors when applied dermally to mice.

Indeno[1,2,3-cd]pyrene is a Group B2 compound - Probable Human Carcinogen based on inadequate evidence in humans and sufficient evidence for carcinogenicity in animal assays (U.S. EPA, 1993).

Oral-to-dermal extrapolation is not appropriate for indeno[1,2,3-cd]pyrene because of the evidence that dermal exposure to indeno[1,2,3-cd]pyrene causes skin cancer and the uncertainty that the oral slope factor will protect against the local carcinogenic effect of dermally applied indeno[1,2,3-cd]pyrene. RAGS HHEM Part 1 (page 7-16) (U.S. EPA, 1989) provides guidance to support this recommendation in the statement that it "is inappropriate to use the oral slope factor to evaluate the risks associated with dermal exposure to carcinogens such as benz[a]pyrene (sic) which cause skin cancer through a direct action at the point of application". Indeno[1,2,3-cd]pyrene and other PAHs are expected to cause skin cancer through a mechanism similar to the mechanism through which benzo[a]pyrene acts.

REFERENCES FOR INDENO[1,2,3-cd]pyrene

ATSDR. 1990. Toxicological Profile for Polycyclic Aromatic Hydrocarbons. Agency for Toxic Substances and Disease Registry. U.S. Public Health Service. Atlanta, GA. Public Comment Draft.

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

U.S. EPA. 1993. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

(6/10/91)

MANGANESE

The oral RfD for manganese (1E-1 mg/kg/day) is based on a NOAEL for CNS effects from human chronic ingestion (dietary and drinking water) of manganese (no LOAEL is reported). Humans have an efficient homeostatic mechanism for maintaining a constant body burden of manganese, as it is an essential element. Liver and gastrointestinal excretory mechanisms are involved in

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elimination of excess manganese; these processes clear 97% of the orally ingested manganese (Newland et al., 1987). There are little data concerning human manganese poisoning; one older study in a population drinking contaminated well water reports lethargy, tremor and mental disturbances. Rodents are not a good animal model for human manganese toxicity, as the neurological endpoints appear to differ from those of humans. A chronic oral study in primates reports muscular weakness at 7 mg/kg/day. Generally little manganese is orally absorbed (3-5%). Absorption may be higher for children, the elderly, pregnant women or those with iron deficiency.

There is also an inhalation RfC on IRIS (4E-4 mg/cu.m.) based on a LOAEL for increased prevalence of respiratory symptoms and psychomotor disturbances in male workers occupationally-exposed to inorganic manganese (manganese dioxide, tetroxide, various salts), which are dusts. These endpoints show both a local irritant effect as well as the same systemic endpoint (CNS) as that from oral exposure (but at very high exposure levels). There are no data on the extent of absorption by inhalation exposure. The lung serves as a depot for manganese, indicating manganese absorption continues beyond the exposure period.

Manganese is classified as an EPA Group D chemical; i.e., not classifiable as to human carcinogenicity, because of the lack of human data and inadequate animal data (U.S. EPA, 1993).

There are no data on dermal absorption in humans or animals, although skin absorption is not considered to occur to a significant extent (U.S. EPA, 1984). ATSDR (1989) reports that dermal manganese exposure, with the exception of potassium permanganate which is corrosive, is not of health concern. It is likely that human occupational exposure encompasses the dermal route, as well as the inhalation route. Available epidemiological information apparently does not mention whether there are any dermal effects reported in individuals exposed by the oral or inhalation routes. Dermal exposure, like inhalation exposure, would bypass the liver (first pass effect) and the gastrointestinal tract, important organs for detoxification. However, it is likely that dermally absorbed manganese would be excreted more rapidly than inhaled manganese. Newland et al. (1987) report faster elimination of brain manganese in monkeys exposed by intravenous or subcutaneous administration than following inhalation exposure. It is likely that the target organ of dermally absorbed manganese would also be the neurological system. Based on the information that little manganese is absorbed by any route, and using the default assumption that since there is no evidence that dermal exposure to manganese will produce effects different from those produced

by oral exposure, it is likely that the oral RfD would be protective for dermal exposure.

REFERENCES FOR MANGANESE:

ATSDR. 1989. Toxicological Profile for Manganese. Draft. Agency for Toxic Substances and Disease Registry. U.S. Public Health Service. Atlanta, GA.

Newland, M.C., Cox, C., Hamada, R., Oberdorster, G., and Weiss, B. 1987. The clearance of manganese chloride in the primate. Fund. Appl. Toxicol. 9(2): 314-328.

U.S. EPA. 1984. Health Assessment Document for Manganese. prepared by the Office of health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1993. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

MERCURY

ENSR assumed that 15% of orally administered inorganic mercury would be absorbed based on data for humans cited in the ATSDR (1989) Toxicological Profile on Mercury. Weiss et al. (1973) reported that 15% of an oral dose of mercuric nitrate in an aqueous solution or bound to calf liver protein was absorbed in humans.

The Drinking Water Criteria Document for Inorganic Mercury (U.S. EPA, 1988) reviewed another report of what is apparently the same study (Rahola et al., 1971). Examination of a more complete report of this study (Rahola et al., 1972) shows that 10 human volunteers were orally administered radiolabeled mercuric nitrate either bound to calf liver protein or in aqueous solution. Whole-body counting of the subjects at various intervals up to 100 days after dose-administration indicated that 1.4% to 15.6% of the doses were retained by the body (an overall average of 7% retention was reported). Radioactivity in feces collected for 4-5 days after administration accounted for about 85% of the administered radioactivity; radioactivity in urine accounted for only 0.2%. These data indicate that ENSR's assumed value of 15% is an appropriate upper boundary on the available estimates for oral absorption efficiency of inorganic mercury in humans. It should be noted, however, that an unknown amount of the radioactivity excreted in the feces could have been absorbed and then eliminated in the bile.

Data for animals reviewed by ATSDR (1989) and the EPA (1988) indicate that the extent of oral absorption may be less than 15%. Clarkson (1971) reported that 1-2% of an oral dose of mercuric chloride was absorbed by mice. Another study measured 38% absorption of oral doses of mercuric chloride in one-week-old mice, 1% in adult mice on a standard diet, and 7% in adult mice on a milk diet (Kostial et al., 1978).

In summary, ENSR's assumed value of 15% oral absorption for inorganic mercury appears to be justifiable as an upper boundary estimate for humans and to be within RAGS HHEM Part A guidelines (U.S. EPA, 1989).

ENSR's proposed value of 0.1% dermal absorption for inorganic mercury in sediment is the default value for inorganics in soil recommended by the Massachusetts DEQE (1989). Quantitative data for the extent of absorption of inorganic mercury salts by skin are not available in reviews by the ATSDR (1989) or the U.S. EPA (1988). Dermal absorption is expected to occur based on clinical case studies of mercury intoxication in humans following dermal application of ointments containing inorganic mercury salts (ATSDR, 1989). Data on the dermal absorption of inorganic mercury were not reviewed by the U.S. EPA (1988). In the absence of quantitative data on the extent of dermal absorption of mercury, ENSR's assumed value of 0.1% appears to be a reasonable estimate based upon analogy to other inorganic metallic salts (see previous discussions in this document on barium and cadmium).

REFERENCES FOR MERCURY

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Mercury. ATSDR, U.S. Public Health Service, Atlanta, GA. NTIS PB/90/181256/AS.

Clarkson, T.W. 1971. Epidemiological and experimental aspects of lead and mercury contamination of food. Food Cosmet. Toxicol. 9: 229-243. Cited in U.S. EPA 1988.

DEQE (Massachusetts Department of Environmental Quality Engineering). 1989. Guidance for Disposal Site Risk Characterization and Related Phase II Activities. In Support of the Massachusetts Contingency Plan. Office of Research and Standards. Report #70.

Kostial, K., D. Kello, S. Jugo, I. Rabar and T. Maljkovic. 1978. Influence of age on metal metabolism and toxicity. Environ. Health Perspect. 25: 81-86. Cited in U.S. EPA, 1988.

Rahola, T., T. Hattula, A. Korlainen and J.K. Miettinen. 1971. The biological halftime of inorganic mercury (Hg^{2+}) in man. Scand. J. Clin.-Invest. 27 (suppl. 116): 77. (Abstract). Cited in U.S. EPA, 1988.

Rahola, T., R-K. Aaran and J.K. Miettinen. 1972. Half-time studies of mercury and cadmium by whole-body counting. In: Assessing Radioactive Contamination in Man. Proceedings of a symposium on assessment of radioactive organ and body burdens. International Atomic Energy Agency, Vienna. pp. 553-562.

U.S. EPA. 1988. Drinking Water Criteria Document for Mercury. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/X-84/178

U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Volume 1. Human Health Evaluation Manual (Part A). Prepared by the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-89/002.

Weiss, S.H., J.R. Wands and J.H. Yardley. 1973. Demonstration by electron defraction of black mercuric sulfide ($b-HgS$) in a case of "melanosis coli and black kidneys" caused by chronic inorganic mercury poisoning [Abstract]. Lab. Invest. p. 401-402. Cited in ATSDR, 1989.

(4/06/92)

Mercury

In response to your request we asked the Exposure Assessment Group (EAG) to review the dermal absorption factors for mercury developed by the Massachusetts Department of Environmental Protection, which you provided. The review, conducted by Karen Hammerstrom, is attached. Briefly, EAG suggests dermal absorption factors of 4%, 5%, and 5% for elemental, inorganic, and methyl mercury, respectively. In her review, Karen refers to a memo from Syracuse Research Corporation prepared in response to an earlier request for information on mercury; this memo is also attached for your information.

Attached please find the following information:

SECTION 1:

Exposure Assessment Group (EAG) review of the dermal absorption factors for mercury. Provide by Karen Hammerstrom

(located after page 31)

SECTION 2:

John Schaum's comments on the dermal absorption assessment of mercury provided by Syracuse Research Corporation.

(located after pg 81)

SECTION 3:

Syracuse Research Corporation's dermal absorption assessment of mercury.

Section 3

Dermal absorption of Hg^0 from soil

In the absence of empirically derived NOAELs and LOAELs for dermal exposure, the procedure that is recommended for characterizing non-cancer risk associated with dermal exposure (i.e., hazard quotient) is to compare the oral RfD that has been adjusted for absorption to the estimated absorbed dose associated with dermal exposure. The dose absorbed through the skin is estimated as follows (U.S. EPA, 1989):

$$AD = (CS)(CF)(SA)(AF)(ABS)(EF)(ED)/(BW)(AT) \quad \text{Eq. 2}$$

where

AD	=	absorbed dose (mg/kg-day)
CS	=	concentration of chemical in soil (mg/kg)
CF	=	conversion factor (10^{-6} kg/mg)
SA	=	exposed skin surface area (cm^2)
AF	=	soil-to-skin adherence factor (mg/ cm^2)
ABS_d	=	soil dermal absorption factor (unitless)
EF	=	exposure frequency (events/year)
ED	=	exposure duration (years)
BW	=	body weight (kg)
AT	=	averaging time (period over which exposure is averaged; e.g., days)

Dermal absorption factor (ABS_d): There are no published quantitative studies of dermal absorption of Hg^0 from soil thus, the ABS_d must be derived indirectly from related empirical data and theoretical considerations (Computerized searches of TOXLINE for studies of bioavailability of mercury from soil were conducted; no pertinent cites were found). A simple model of soil Hg^0 on the skin surface has Hg^0 partitioned into free and bound compartments. Bound Hg^0 (B) includes Hg^0 that is strongly sorbed to soil and not available for absorption into the systemic circulation. Free Hg^0 (F) is not strongly sorbed to soil and is available for contact with the skin and absorption.

$$T_{Hg} = B_{Hg} + F_{Hg} \quad \text{Eq. 3}$$

$$\text{where } F_{\text{Hg}} = T_{\text{Hg}}(1-\text{SF}) \quad \text{Eq. 4}$$

T_{Hg} = total amount of mercury in soil that has adhered to skin (mg)
 B_{Hg} = bound mercury in soil that has adhered to skin (mg)
 F_{Hg} = free mercury in soil that has adhered to skin (mg)
 SF = sorption factor (unitless)

The soil dermal absorption factor (ABS_d) can be defined as the product of the dermal absorption factor for free Hg^0 that comes in direct contact with the skin surface (AB_d), the free Hg^0 soil-to-skin transport factor (TF) and the inverse of the soil sorption factor (SF), as follows:

$$\text{ABS}_d = (\text{AB}_d)(\text{TF})(1-\text{SF}) \quad \text{Eq. 5}$$

$$\text{ABS}_d = (0.4)(1)(0.1)$$

$$\text{ABS}_d = 0.04$$

where

ABS_d = soil dermal absorption factor
 AB_d = dermal absorption factor for free Hg^0 deposited on the skin surface (0.4)
 TF = free Hg^0 soil-to-skin transport factor
 SF = sorption factor (0.1)

Estimates of the free Hg^0 absorption factor (AB_d): The value of 0.4 for AB_d is based on studies of Hursh et al. (1989), in which human volunteers were exposed to Hg^0 by placing their forearms in a $^{203}\text{Hg}^0$ vapor atmosphere. The range of exposure durations for individual subjects was 27-43 minutes; the range of exposure concentrations was 0.88-2.14 mg/m³ (static exposure in 0.009 m³ exposure volume). Deposition and retention of ^{203}Hg on the forearm skin and in the whole body was quantified for several weeks after exposure. Deposition was 0.01-0.04 ng Hg/cm^2 skin per ng Hg/cm^3 air (approximately 1-5% of total exposure). Of the total amount of mercury deposited on the forearm (216 - 844 ng Hg , five subjects), approximately 40% was absorbed into the systemic circulation (26-45%); the remaining mercury was retained in the epidermis and eventually shed in desquamated cells. Systemic uptake of mercury occurred over a period of several days (e.g., at least 10 days), suggesting the likelihood of oxidation of Hg^0 to Hg^{2+} in the skin and slow release into the circulation,

rather than a rapid diffusion of Hg^0 through the skin; the latter being more characteristic of alveolar absorption of inhaled Hg^0 .

In the model described in Equation 5, an absorption factor of 0.4 is assumed for free Hg^0 that makes direct contact with the skin surface; i.e., free Hg^0 that comes into direct contact with skin is assumed to behave in a quantitatively similar manner as the mercury vapor that deposited on the forearms of the subjects in the Hursh et al. (1989) study. Note that the Hursh et al. (1989) study does not accurately simulate the skin contact that would result from adherence of soil to the skin and therefore can not be used to estimate the amount of free Hg^0 in soil that would come into direct contact with the skin.

Estimate of free Hg^0 soil-to-skin transport factor (TF): The soil-to-skin transport factor reflects the fractional amount of free Hg^0 in soil adhered to skin that comes into direct contact with the skin surface. Free Hg^0 in soil can exist in the vapor or liquid state. Since mercury vapor can diffuse from the soil away from the skin without first being deposited on the skin surface, the TF has a value less than 1; how much less than one will depend on numerous factors, including the Hg^0 vapor concentration in the interstitial spaces of the soil and other factors that determine volatilization of Hg^0 from soil and diffusion of Hg^0 at the skin air interface (see Section II). The upper bound value of 1 for TF is assumed in Equation 5; a lower value for this parameter would decrease the estimated value of the dermal absorption factor (ABS_d).

Estimate of sorption factor (SF): As noted above, Hg^0 can exist in the vapor state, in the sorbed state, or in the liquid state in soil. According to Landa (1978), the saturation concentration of Hg^0 in soil from a vapor phase concentration of $15 \mu\text{g}/\text{m}^3$ would be $50 \mu\text{g}/\text{kg}$ soil (50 ppb). If the vapor phase concentration of Hg^0 in the interstitial spaces of soil is less than $15 \mu\text{g}/\text{m}^3$, about 56% will remain sorbed in the soil, and the rest will exist in the vapor phase. If the vapor phase concentration of Hg^0 in the interstitial soil spaces exceeds its saturation sorption capacity, the amount exceeding the capacity will remain unsorbed and be available for inhalation and dermal contact. Landa (1978) exposed five Montana soils to Hg^0 vapor at a concentration of $15 \mu\text{g}/\text{m}^3$ for a sufficient period of time to achieve saturation, and then attempted to extract the mercury by treating the soils with various chemical extractant. Vaporization of the mercury, without extraction, was negligible. Extraction with distilled water or dilute KCl or CaCl_2 solutions was less than 1%. Less than 10% of sorbed mercury could be removed from soil (including soil that had 74% sand and 12% clay).

with such complexing agents as 0.5 M acetylacetone and 0.5 M cupferron (Landa, 1978). Thus, greater than 90% of the mercury was strongly sorbed to the soil. Based on the Landa (1978) study, a value of 0.9 has been assumed for the soil sorption factor. This should be considered to be an upper bound estimate for soil that has been exposed to Hg^0 , however, the value for SF may vary with the soil type and exposure scenario; i.e., the sorption factor for liquid Hg^0 mixed with soil may not be the same as that for soil exposed to Hg^0 vapor.

Conclusions: Based on the above considerations, a value of 0.04 is estimated to be the soil dermal absorption factor (ABS_d). The 0.04 absorption factor applies only to Hg^0 sorbed to soil; Hg^0 vapor present in the interstitial spaces of soil could be inhaled, and both sorbed and free Hg^0 in soil deposited on the skin (e.g., hands and face) could be ingested.

REFERENCES FOR MERCURY

Hursh, John B., Thomas W. Clarkson, Ellen F. Miles and Lowell A. Goldsmith. 1989. Percutaneous Absorption of Mercury Vapor by Man. Arch of Environmental Health. 44: 120-127.

Landa, E.R. 1978. The retention of metallic mercury vapor by soils, Geochem. Cosmochim. Acta. 42: 1407-11.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Volume 1. Human Health Evaluation (Part A). Office of Emergency and Remedial Response, Washington, DC. Interim Final EPA/540/1-89/002.

(6/05/92)

NICKEL

The verified RfD for soluble salts of nickel is $2E-2$ mg Ni/kg/day (U.S. EPA, 1992). The critical effect was decreased body and organ weights in a chronic rat dietary study; a subchronic gavage study in rats with nickel in water provided support for the principal study (U.S. EPA, 1992). The RfD is not medium-specific, and (as noted by ENSR) is based on an administered dose. Therefore, the appropriate value of the AAFs for the three oral exposure scenarios at the Yaworski Lagoon site is 1.

ENSR reviewed absorption data for humans and animals indicating that the percentage oral absorption of soluble nickel salts is influenced by (i.e., decreased by) adsorption to dietary components and soil (pages 1-43 through 1-47). This assessment

(Continues after mercury sections 1 and 2)

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Section 1

7.2.96

United States Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment (RD-689)
Exposure Assessment Group
401 M Street SW
Washington, DC 20460
(202) 260-8919
FAX No. (202) 260-1722

March 27, 1992

MEMORANDUM

SUBJECT: Review of dermal absorption values for mercury
requested by Ann-Marie Burke, Region I

TO: Joan Dollarhyde, ECAO

FROM: Karen A. Hammerstrom *Karen A. Hammerstrom*
Environmental Scientist

This is in response to the FAX of March 13, 1992, from the Superfund Support Center. Region I requested a review of dermal absorption factors (but not the oral absorption factors) developed for mercury compounds by the Massachusetts Department of Environmental Protection. Three factors were developed -- 2% for elemental mercury, 1% for inorganic salts, and 77% for methyl mercury.

I am assuming that these factors will be used only for assessments of mercury in soil or sediment and that a permeability coefficient will be used to estimate exposure to mercury in water.

Elemental Mercury

The Exposure Assessment Group (EAG) has not conducted a literature search on elemental mercury. However, in a memo dated October 18, 1991, to Cindy Sonich-Mullin from Gary Diamond and Dipak Basu, Syracuse Research Corporation provided an assessment of elemental mercury in which they based the dermal absorption factor for soil on the data in Hursh et al. (1989). SRC used the data in Table 2 of Hursh et al. (1989), which report maximum systemic mercury as a fraction of initial amount of mercury measured on the skin after the end of exposure. The initial amounts of mercury on the skin are reported in Table 1 in the column headed S_0 . SRC calculated an average percentage absorbed of 40% of free mercury deposited on the skin from data obtained from 5 human volunteers by Hursh et al. (1989). SRC then

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Section 1 of 1 - Mercury

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estimated that a maximum of 10% of the mercury in soil could be extracted and available for dermal absorption based on experiments conducted by Landa (1978), and arrived at a dermal absorption factor of 4%.

I think that SRC's analysis provides a better estimate than the MADEP's analysis. The MADEP's analysis is flawed. It appears that MADEP has adjusted the data by assuming that the ratio (percent of total absorbed dose entering by the dermal route to percent of total absorbed dose entering by the inhalation route) is directly proportional to the ratio (percent of dermally applied dose absorbed to percent of inhaled dose absorbed). This is obviously not true in this case and would be true only in the very unlikely case that the dermally applied dose and the dose administered by inhalation were equal.

Inorganic Mercury

The Region did not provide MADEP analysis of the dermal absorption factor and references for inorganic mercury, which are apparently contained in a discussion of chromium elsewhere in the risk assessment. The upper bound is postulated as 1%.

One of our contractors, ENSR, did a literature search for dermal absorption of inorganic mercury and based their analysis, in part, on the results reported in Skog and Wahlberg (1964). Skog and Wahlberg studied absorption of mercuric chloride, K_2HgI_4 , and methyl mercury applied in aqueous solutions of 320 $\mu L/cm^2$ to guinea pigs in vivo. (See paper for dose levels). For both inorganic and organic compounds, absorption over 5 hours ranged from about 2% to 5% of the applied dose. Assuming that the Landa (1978) data on extractability of metallic mercury from soil apply to inorganic mercury as well, a maximum of 10% of the inorganic mercury in soil will be available for dermal absorption. In this case, an estimate of 1% of applied dose absorbed from soil seems reasonable as a conservative estimate.¹

However, another paper that measured dermal absorption of unbound mercuric chloride in humans suggests a higher absorption factor than 1% for inorganic mercury applied in soil (Baranowska-Dutkiewicz, 1982). This study was not discussed in the draft

¹ENSR examined data in its files on extractability of metals from soil. These data were EP-Tox testing done for RCRA compliance. Maximum percentages of mercury leached from soil were no more than about 3% of the total mercury in the soil and no more than about 5% for any of the other metals reported. I have no information on the form of the mercury, on concentrations of mercury in the soil, on whether the soils were contaminated at levels likely to be found at Superfund sites, or on the characteristics of the soil.

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ENSR literature survey provided to EAG. Nor is it discussed in USEPA (1992), although other studies of chromium and aniline by the same investigators are discussed. I'm not sure why this study was omitted. Aqueous solutions of mercuric chloride were applied to the skin of human volunteers in 250 μ L of water over 22 cm^2 of skin. The area was covered with a watch glass. At the end of the exposure period, which ranged from 5 minutes to 1 hour, the watch glass and skin were washed and the solution was analyzed. The amount absorbed was assumed to be the difference between the applied dose and the amount recovered by washing. The estimated percentages absorbed were about 20 to 65% of the applied dose or about 10 times higher than the percentages reported for guinea pigs by Skog and Wahlberg (1964). These absorption factors are more on the order of the absorption factor of 40% for free mercury determined by SRC from the Hursh et al. (1989) study. Reasons for the differences between Baranowska-Dutkiewicz and Skog and Wahlberg results include differences in dose (doses in Baranowska-Dutkiewicz, on a basis of mg/cm^2 , were lower, and much less water was applied per square centimeter) and differences in species tested. Other reasons for high absorption might be the occlusion by the watch glass or possible losses of material running off the arms of the subjects.

In any event, if the Region wants to be conservative, I think a dermal absorption factor in the range of 5% would be more appropriate, assuming that 10% of the dose applied in soil is the maximum amount of unbound mercury that would be available to be absorbed.

Note on page 225, Baranowska-Dutkiewicz (1982) states, "If we compare the rates of absorption of HgCl_2 (Table 1) with those of Na_2CrO_4 investigated with the same experimental model in humans [Baranowska-Dutkiewicz (1981)], it is evident that Cr^{6+} ions penetrate the skin approximately 30 times slower than the mercury from solutions of HgCl_2 ." Thus, CrVI may not be a good analogue for inorganic mercury.

Methyl Mercury

The Region did not supply MADEP's analysis of dermal absorption of methyl mercury and references, which are apparently contained in the discussion of nickel elsewhere in the risk assessment.

Skog and Wahlberg (1964) studied absorption of methyl mercury applied to guinea pigs in water at two dose levels. The percentages of applied dose absorbed were 3.4% and 4.5%. In the Skog and Wahlberg study, dermal absorption of methyl mercury from water was very similar to absorption of inorganic mercury (see discussion in USEPA, 1992, pages 5-84 to 5-85).

As in the case of inorganic mercury, the dose of methyl

mercury and the amount of water applied to the guinea pig were large and may be the reason the quantity absorbed is small. However, it would probably be safe to assume an absorption of 5% of applied dose rather than the 77%.

Conclusion -

Obviously, there is a great deal of uncertainty in using these numbers. I have not been able to review the Landa paper on extractability of mercury from soil, but, assuming that it appears to represent an upper bound on availability of elemental mercury, inorganic mercury, and methyl mercury, I would use an absorption factor of 5% for all mercury compounds from soil.

EAG has not recommended dermal absorption factors for any chemicals applied in soil at this time except for chlorinated dioxins, chlorinated furans, polychlorinated biphenyls, and cadmium, because of lack of data on which to base recommendations. The above information and analysis is therefore provided only to assist the Region in evaluating the MADEP risk assessment. I am attaching a copy of John Schaums's comments on the SRC paper discussed above in which he points out the lack of data on absorption of mercury from the soil matrix and the uncertainties in extrapolating the Hursh data to the soil exposure scenario. As also pointed out above, however, the MADEP has decided to use the Hursh paper to estimate an upper limit on dermal absorption of elemental mercury from soil. The SRC analysis appears to me to be a much more defensible approach to using these data than the MADEP approach.

EAG has some ongoing projects to improve assessment of absorption of chemicals from soil. More information and insight into these processes may become available as these projects progress. Therefore, we would appreciate an opportunity to comment on any requests for information on this topic from the Regional offices so that we can provide any new information that might assist the Regions in these evaluations.

References

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- Hursh, J.B.; Clarkson, T.W.; Miles, E.F.; Goldsmith, L.A. (1989) Percutaneous Absorption of Mercury Vapor by Man. *Arch. Environ. Health* 44(2):120-127.

8143 Landa, E.R. (1978) The Retention of Metallic Mercury Vapor by Soils. *Geochem. Cosmochim. Acta.* 42:1407-1411.

Skog, B. and Wahlberg, J.E. (1964) A Comparative Investigation of the Percutaneous Absorption of Metal Compounds in the Guinea Pig by Means of the Radioactive Isotopes: ^{51}Cr , ^{58}Co , ^{65}Zn , ^{110m}Ag , ^{115}Cd , ^{203}Hg . *J. Invest. Dermatol.* 43:187-192.

USEPA (1992) Dermal Exposure Assessment: Principals and Applications. Interim Report. Washington, DC: Office of Research and Development, Office of Health and Environmental Assessment, Exposure Assessment Group. EPA/600/8-01/011B.

cc: Kevin Garrahan
Kim-Chi Hoang
John Schaum
Dave Bennett

SUBJECT: Mercury Risk Assessment

FROM: John L. Schaum, Chief
Exposure Assessment Methods Branch (RD-689)

TO: Cindy Sonich-Mullin
ECAO-Cin

I reviewed only Part III: "Dermal Absorption of Hg from Soil" of the document you sent me. The proposed procedure for estimating dermal absorption of mercury in soil appears quite innovative and interesting as an avenue of research. However, it is highly speculative and we really have no idea how valid it is. In preparing our dermal document, we concluded that firm recommendations could not be made for dermal absorption from soil for a number of chemicals with much stronger data than this. I would much rather see this kind of proposal published as a research paper and peer reviewed before applying it to real sites. Until better data are available for validating these type of procedures, I suspect we are generally better off conducting assessments of dermal exposure to soil in a more qualitative fashion. For example, we may want to advise the program that dermal contact with mercury is probably comparable or less important than other exposure pathways such as soil ingestion. This is based on facts that this preliminary assessment indicated a low absorption fraction and that the only tested metal in soil (ie. Cd) has relatively low absorption.

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C. H. in 2 - Mercury

is in agreement with reviews by the U.S. EPA (1986) and the ATSDR (1988; 1991). In general, the values in the reviewed studies ranged from approximately 1 to 10%; values at the high end of this range were identified in fasted individuals, while values at the low end were for absorption in the presence of food or soil. For the purposes of characterization of the risk associated with dermal exposure scenarios at the Yaworski Lagoon site, a general fractional oral absorption value of 0.1 is recommended for soluble nickel salts. This value represents an upper boundary of the range of empirical estimates, and as such is conservatively protective as per guidelines in RAGS HHEM Part A (U.S. EPA, 1989).

The U.S. EPA (1986) did not identify any data regarding the fractional dermal absorption of nickel. In contrast, ATSDR (1988; 1991) reviewed data that show that nickel is absorbed by the skin. Norgaard (1955) reported that 55-77% of an occluded radioactive dose of nickel sulfate was absorbed within 24 hours, but it could not be concluded whether the nickel had been absorbed into the deep layers of the skin or into the bloodstream. Fullerton et al. (1986) reported that 0.23% of an applied non-occluded dose of

nickel chloride permeated excised human skin, while 3.5% permeated occluded skin. Lloyd (1980) reported that 0.005 to 0.51% of dermally applied radioactive nickel chloride was absorbed by guinea pigs as indicated by radioactivity in the blood and urine. In general, these data indicate that the extent of dermal absorption of aqueous solutions of nickel salts is likely to be small (0.005 to 0.51% for non-occluded conditions). Due to adsorption to soil particles, dermally applied nickel in soil is likely to be absorbed to an even lesser degree. ENSR cited a value of 0.08% for the fractional absorption of nickel in soil; the basis for this value was not explained, but was cited to "ENSR, 1992" -- this reference was not listed in the reference section of the ENSR document.

It is recommended that the approximate midpoint of the range for percentage dermal absorption of aqueous nickel solutions in guinea pigs reported by Lloyd (1980), 0.05%, be used by ENSR for risk characterization of the dermal-soil exposure scenario. The upper end of the reported range (0.51%) is not recommended because soil adsorption is likely to restrict dermal absorption relative to the conditions provided by Lloyd (1980). It should be noted that this recommended value is close to the value proposed by ENSR (0.08%), but the basis of ENSR's proposed value was not provided.

REFERENCES FOR NICKEL

ATSDR. 1988. Toxicological Profile for Nickel. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

ATSDR. 1991. Updated Toxicological Profile for Nickel. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. Draft for Public Comment.

Fullerton, A., J.R. Anderson, A. Hoelgaard and T. Menne. 1986. Permeation of nickel salts through human skin in vitro. Contact Derm. 15: 173-177. Cited in ATSDR, 1991.

Lloyd, G.K. 1980. Dermal absorption and conjugation of nickel in relation to the induction of allergic contact dermatitis - preliminary results. Cited in ATSDR, 1991.

Norgaard, O. 1955. Investigation with radioactive Ni-57 into the resorption of nickel through the skin in normal and in nickel-hypersensitive persons. Acta. Derm. Venereol. 35: 111-117. Cited in ATSDR, 1988, 1991.

U.S. EPA. 1986. Health Assessment Document for Nickel and Nickel Compounds. Office of Health and Environmental Assessment, Washington, DC. EPA/600/8-83/012FF.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Volume 1. Human Health Evaluation Manual (Part A). Prepared by the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-89/002.

U.S. EPA. 1992. Integrated Risk Information System (IRIS). Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH.

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(6/05/92)

NICKEL

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The U.S. EPA (1986) did not identify any data regarding the fractional dermal absorption of nickel. In contrast, ATSDR (1988; 1991) reviewed data that show that nickel is absorbed by the skin. Norgaard (1955) reported that 55-77% of an occluded radioactive dose of nickel sulfate was absorbed within 24 hours, but it could not be concluded whether the nickel had been absorbed into the deep layers of the skin or into the bloodstream. Fullerton et al. (1986) reported that 0.23% of an applied non-occluded dose of nickel chloride permeated excised human skin, while 3.5% permeated occluded skin. Lloyd (1980) reported that 0.005 to 0.51% of dermally applied radioactive nickel chloride was absorbed by guinea pigs as indicated by radioactivity in the blood and urine. In general, these data indicate that the extent of dermal absorption of aqueous solutions of nickel salts is likely to be small (0.005 to 0.51% for non-occluded conditions). Due to adsorption to soil particles, dermally applied nickel in soil is likely to be absorbed to an even lesser degree.

It is recommended that the approximate midpoint of the range for percentage dermal absorption of aqueous nickel solutions in guinea pigs reported by Lloyd (1980), 0.05%, be used by ENSR for risk characterization of the dermal-soil exposure scenario. The upper end of the reported range (0.51%) is not recommended because soil adsorption is likely to restrict dermal absorption relative to the conditions provided by Lloyd (1980).

REFERENCES FOR NICKEL

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Lloyd, G.K. 1980. Dermal absorption and conjugation of nickel in relation to the induction of allergic contact dermatitis - preliminary results. Cited in ATSDR, 1991.

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U.S. EPA. 1986. Health Assessment Document for Nickel and Nickel Compounds. Office of Health and Environmental Assessment, Washington, DC. - EPA/600/8-83/012FF.

(2/11/92)

Phenanthrene

Human data regarding carcinogenic or noncarcinogenic effects following inhalation, oral or dermal exposure were not available. However, phenanthrene can be a component of mixtures (e.g. tobacco smoke, coal tar, soots and coke oven emissions) that have been associated with human cancer.

Animal studies examining noncarcinogenic effects following administration of phenanthrene by any route are not available except for a report of hepatotoxic effects in rats following an acute intraperitoneal injection.

Phenanthrene is classified to be a Group D carcinogen - probable human carcinogen based on the availability of no human data and insufficient data from animal tests (U.S. EPA, 1992). Only one out of five suitably designed available mouse skin-painting assays for tumor-initiation activity produced a carcinogenic response. The only other available animal studies (a rat gavage study and another mouse skin application study) produced no carcinogenic responses, but the data were inconclusive because of design inadequacies.

In the absence of unequivocal data to indicate that phenanthrene is a skin carcinogen or produces other effects at sites of dermal application, oral-to-dermal extrapolation appears appropriate.

REFERENCES FOR PHENANTHRENE:

U.S. EPA. 1990. Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons (PAHs). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

U.S. EPA. 1993. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

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ATSDR (Agency for Toxic Substances and Disease Registry). 1990.
Toxicological Profile for Polycyclic Aromatic Hydrocarbons.
U.S. Public Health Service. Atlanta, GA.

PHENOL

(6/5/92)

ENSR assumed a value of 10% for the extent of dermal absorption of phenol in soil based upon the report that about 13% of applied dermal doses of aqueous solutions of phenol were absorbed by human volunteers in 30 minutes (Baranowska-Dutkiewicz, 1981) and that the efficiency of dermal absorption from soil at the Yaworski site would be expected to be less due to soil adsorption and phenol volatilization from the skin.

ENSR's assumed value for dermal absorption of phenol in soil does not appear to be conservatively protective based upon the available data. Baranowska-Dutkiewicz (1981) reported that the rate of dermal absorption was constant during a 1-hour exposure period and that the absorbed percentage of an applied dose allowed on the skin for 1 hour (22.7%) was almost twice that observed for a 30-minute exposure (12.6%). Extrapolation of the Baranowska-Dutkiewicz (1981) data to a 6- or 12-hour exposure scenario, therefore, suggests that 100% absorption would occur. The exposed area of the skin in these experiments was covered with a watch glass thereby limiting volatilization of phenol from the skin. Comparison of the vapor pressure of phenol at 25 C (0.41 mm Hg, Riddick et al., 1986) with that of benzene (95.2 mm Hg, Riddick et al., 1986), however, provides suggestive evidence that the volatility of phenol may not be sufficiently great to significantly diminish its dermal absorption efficiency. Benzene's volatility has been demonstrated to drastically diminish its dermal absorption. The extent to which soil adsorption of phenol limits the dermal absorption of phenol is unknown. Because the degrees to which volatilization and soil adsorption will diminish the dermal absorption efficiency for phenol are unknown, it is recommended that a value of 100% dermal absorption be used for phenol in sediment or soil in order to be conservatively protective.

REFERENCES FOR PHENOL

Baranowska-Dutkiewicz, B. 1981. Skin absorption of phenol from aqueous solutions in men. Int. Arch. Occup. Environ. Health 49: 99-104.

Riddick, J.A., W.B. Bunger and T.K. Sakano. 1986. Techniques of Chemistry, Vol. II. Organic Solvents. John Wiley and Sons, New York.

(6/10/91)

SILVER

The oral RfD on IRIS, 3E-3 mg/kg/day (flagged as pending change), is based on the LOAEL for argyria (bluish discoloration of the skin and cornea) in humans from therapeutic administration of silver. A study in rats shows decreased body weight gain following oral administration of silver (details not provided) (ATSDR, 1989).

Silver is classified as an EPA Group D compound, not classifiable as to human carcinogenicity, based on no human data and inadequate animal data (U.S. EPA, 1993).

Prolonged dermal exposure (not quantified) to silver can produce discoloration of the skin. In addition, allergic reactions, presumably at the site of contact, have been reported following repeated dermal contact such as with dental fillings and radiographic processing solutions (ATSDR, 1989b). The only study of systemic toxicity of silver following dermal exposure in animals reported that when 2.0 ml of 0.239 molar silver nitrate in water was applied by skin depot for 8 weeks, guinea pigs showed decreased weight gain (-10-21%) relative to vehicle and untreated controls.

While both oral and dermal exposure to silver produces argyria, dermal exposure may also produce an allergic reaction. It is not known whether the oral RfD would protect against possible sensitization, although the available oral data do not indicate any allergic reactions and the dermal allergic reaction appears to be at the site of contact. However, to be protective of human health, a route-to-route extrapolation is not recommended based on the lack of information of possible immunological effects produced following oral exposure, and the possibility of a dermal route-specific contact sensitization.

REFERENCES FOR SILVER:

ATSDR. 1989. Toxicological Profile for Silver. Draft for Public Comment. Agency for Toxic Substances and Disease Registry. U.S. Public Health Service. Atlanta, GA.

U.S. EPA. 1993. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

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Toluene

(10/09/92)

As reviewed by the U.S. EPA (1990), data are available for animals and humans that indicate that toluene can be absorbed through the skin. Jakobson et al. (1982) reported that peak levels of toluene in blood were reached within 6 hours of application of liquid toluene to a sealed area of the dorsal skin of guinea pigs. Tsuruta (1982) reported that 431 ug of an applied dose of 1 ml of toluene (approximately 867 ug toluene applied) penetrated a 2.55 cm² area of excised rat skin within 5 hours in a diffusion cell. Dutkiewicz and Tyras (1968a,b) measured dermal absorption rates of 160-600 ug/cm²/hr and 14-23 mg/cm²/hr when human volunteers immersed both hands in aqueous solutions of toluene and when liquid toluene was applied to the forearm of subjects, respectively. Recently, Morgan et al. (1991) reported that 28% of a 2 ml dose of toluene was absorbed within 24 hours of application to a sealed 3.1 cm² area of the dorsal skin of rats.

Quantitative data on the extent of dermal absorption when toluene (as a pure liquid or in soil) is applied to uncovered skin are not available. The vapor pressure of toluene (28.7 mm Hg at 25 C; U.S. EPA, 1990), however, indicates that volatilization will significantly diminish the extent of dermal absorption (relative to occluded conditions), but likely not to the same extent as the absorption of benzene which has a higher vapor pressure (92.5 mm Hg at 25 C). As discussed previously in this document, the extent of dermal absorption of benzene when applied to uncovered human skin is 0.05%, in contrast to nearly 100% absorption under sealed conditions (Skowronski et al., 1988; Franz, 1984). In the absence of direct data, the "proposed value" of 3% appears to be a reasonably conservative estimate for the dermal absorption efficiency of toluene in soil; no change is recommended. The surrogate use of benzene's recommended absorption value is not suggested, because toluene's lower vapor pressure indicates that less volatilization may occur when it is applied to uncovered skin than when benzene is applied to uncovered skin.

As reviewed by U.S. EPA (1984), fractional oral absorption data are available from rabbit studies with toluene. El Masry et al. (1956) and Smith et al. (1954) reported that urinary excretion of metabolites and respiratory exhalation accounted for 92-99% of orally administered toluene in rabbits, thereby indicating nearly complete absorption of toluene. More recent reviews by ATSDR (1989) and the U.S. EPA (1990) did not identify new data for oral absorption in animals or humans. Based on the rabbit data, a value of 100% is recommended to adjust oral toxicity values for toluene to an absorbed dose basis.

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Justification for the "proposed value" of 1% was not provided in the Dirk's Farm document.

REFERENCES FOR TOLUENE

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological Profile for Toluene. ATSDR, U.S. Public Health Service, Atlanta, GA. NTIS PB/90/198904/AS.

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Franz, T.J. 1984. Percutaneous absorption of benzene. Adv. Modern Environ. Toxicol. Vol. 6. Applied Toxicology of Petroleum Hydrocarbons. Princeton Scientific Publishers, Inc., Princeton, NJ. p. 61-70.

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Skowronski, G.A., R.M. Turkall and M.S. Adbel-Rahman. 1988. Soil adsorption alters bioavailability of benzene in dermally exposed male rats. Am. Ind. Hyg. Assoc. J. 49(10): 506-511.

Tsuruta, H. 1982. Percutaneous absorption of organic solvents. III. On the penetration rates of hydrophobic solvents through

the excised rat skin. Ind. Health. 20(4): 335-345. Cited in U.S. EPA, 1990.

U.S. EPA. 1984. Health Effects Assessment for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86/033. NTIS PB86-134442/AS.

U.S. EPA, 1990. Drinking Water Criteria Document for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/X-90/240.

(6/05/92)

VANADIUM

Data on the rate or extent of dermally applied vanadium compounds were not reviewed by the U.S. EPA (1987). The ATSDR (1990) did not locate data on the rate or extent of dermal absorption of vanadium, but commented that the dermal absorption is generally expected to be very low like that of other metals with low solubility. ENSR assumed a value of 0.1% for the dermal absorption of vanadium from soil; this value was recommended by the Massachusetts Department of Quality Engineering as a default value for the dermal absorption of inorganics in soil (DEQE, 1989). In the absence of data for vanadium and in consideration of the poor efficiency of dermal absorption of other metallic cations from soil, ENSR's proposed value appears reasonable and within RAGS HHM Part A guidelines.

REFERENCES FOR VANADIUM

ATSDR. 1990. Toxicological Profile for Vanadium. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. Draft for Public Comment.

DEQE (Massachusetts Department of Environmental Quality Engineering). 1989. Guidance for Disposal Site Risk Characterization and Related Phase II Activities. In Support of the Massachusetts Contingency Plan. Office of Research and Standards. Report # 70.

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U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Volume 1. Human Health Evaluation Manual (Part A). Prepared by the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-89/002.

(10/09/92)

Xylene

Quantitative data for the extent of absorption of dermally applied xylene were not reviewed in U.S. EPA documents (1984; 1985; 1989) or by the ATSDR (1990), however there are data that show that dermally applied xylenes can be absorbed. Engstrom (1977) and Riihimaki (1979) measured dermal absorption rates of 100 to 120 ug/cm²/hr based on urinary excretion of xylene metabolites by human volunteers who immersed both hands in m-xylene for 15 minutes. Dutkiewicz and Tyras (1968) measured dermal absorption rates of 4.5 to 9.6 mg/cm²/hr in human volunteers who had 1 ml of liquid xylene applied to a sealed area of skin on their forearms for 1 hour. Tsuruta (1982) reported that 59.4 ug o-xylene penetrated a 2.55 cm² area of excised rat skin within 5 hours in a diffusion cell; a penetration rate of 6.2 ug/cm²/hr was calculated. Recently, Morgan et al. (1991) reported that 32.5% of a 2 ml quantity of m-xylene was absorbed within 24 hours of application to a sealed 3.1-cm² area of the dorsal skin of rats. Quantitative data on the extent of absorption for xylene applied to uncovered skin (either undiluted or in soil) are not available, but volatilization is expected to diminish absorption to some degree. The vapor pressures of xylene isomers (5-6.5 mm Hg at 25; U.S. EPA, 1985) are considerably less than the vapor pressure of benzene (95.2 mm Hg at 25 C), thereby indicating that the degree of volatilization would be less for xylene isomers than for benzene. As discussed in the benzene entry in this document, more than 99% of undiluted benzene applied to skin was shown to be volatilized.

In the absence of data for xylene, the "proposed dermal absorption value" of 3% is recommended for use in estimating absorbed doses from dermal exposure to styrene in soil, rather than adopting the recommended value for benzene of 0.05%. The decision to not use the benzene value is based on the difference in vapor pressures between the two substances.

U.S. EPA (1984) cited data from rabbit studies (Bray et al., 1949) indicating that 85-90% of administered oral doses of xylene isomers was recovered as metabolites in the urine of rabbits; the

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studies did not quantify the extent of respiratory exhalation or compound remaining in the body. Thus, 90% represents an estimate of a minimum extent of uptake in these studies. Additional data regarding the extent of absorption of orally administered xylene were not cited in more recent reviews (U.S. EPA, 1989; ATSDR, 1990). The "proposed value" of 0.90 for adjusting the oral RfD for xylene to an absorbed dose basis is reasonably consistent with the animal data and is recommended herein.

REFERENCES FOR XYLENE

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Toxicological Profile for Total Xylenes. ATSDR, U.S. Public Health Service, Atlanta, GA.

Bray, H.G., B.G. Humphries and W.V. Thorpe. 1949. Metabolism of derivatives of toluene: 3. O-, m-, and p-xylenes. Biochem. J. 45: 241-244. Cited in U.S. EPA, 1985.

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Zinc

(10/09/92)

No quantitative information on the absorption efficiency of dermally applied zinc was located in ATSDR (1989) or U.S. EPA (1980, 1984), but dermal absorption of zinc has been reported to occur in burn patients treated with zinc oxide and in rat skin to which zinc salts were applied. In the absence of quantitative data for zinc and in consideration of the poor efficiency of dermal absorption of other metallic cations in aqueous solutions (Shah and Guthrie, 1986), as well as consideration of the propensity for cations to adsorb soil particles, a value of 1% is recommended for dermal absorption of zinc. This value is consistent with those recommended herein for other inorganic cations without quantitative data for dermal absorption. The basis of the "proposed value" of 0.13 was not discussed in the Dirk's Farm document.

As reviewed by the U.S. EPA (1980; 1984) and the ATSDR (1989), the absorption of zinc from the gastrointestinal tract is dependent on several factors including the chemical form of zinc, the presence of other chemicals and the zinc status of the organism. A high concentration of phytate and dietary fiber will decrease the absorption of zinc; zinc associated with animal protein in the diet (meat, milk, eggs) is thought to be more efficiently absorbed than zinc in vegetable tissue. ATSDR (1989) reported that approximately 20-30% of all ingested zinc is absorbed. NAS (1989) used an absorption factor of 20% for its calculation of the recommended dietary allowance (RDA) for zinc. The 20% absorption factor was used to take into account the lower absorption of zinc from fiber rich diets as compared to the higher absorption in meat-containing meals. Based on this information, an oral absorption efficiency value within the reported range of 20% to 30% is recommended for adjustment of the oral RfD to an absorbed-dose basis. The "proposed value" of 0.25 appears consistent with this recommendation and the data reviewed in Agency documents (U.S. EPA, 1980; 1984) and the ATSDR Toxicological Profile on Zinc; no change is recommended.

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Attachment U**5747**

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
RESEARCH AND DEVELOPMENT

March 18, 1993

MEMORANDUM

SUBJECT: Review of Position Paper on Proposed Modifications to
Soil Clean-Up Levels, American Chemical Services Site,
Griffith, Indiana, EPA ID IND016360265

FROM: Karen A. Hammerstrom *Karen A. Hammerstrom*
Environmental Scientist
Exposure Assessment Group (RD-689)

TO: Joan Dollarhide
ECAO

As requested, I have reviewed Appendix A, "Development of
Dermal Absorption Estimates," in the above submission.

As the author of Section 6, of *Dermal Exposure Assessment: Principles and Applications* ("DEA"), I can state that the authors have misread, misstated, and misapplied that document in just about every argument in Appendix A. DEA is not a guidance document. Rather it is a compendium of currently available data on percutaneous absorption of chemicals from water and soil and is intended to assist Superfund risk assessors in developing exposure estimates. Data are very sparse on absorption from soil and only a very few chemical-specific absorption fractions are recommended in section 6. As I understand OERR's current practice, the Regions are continuing to make chemical-by-chemical determinations or to use default values for classes of chemicals. The Region's default values of 30% for SVOCs, 30% for VOCs, and 1% for inorganics seem reasonable and in accord with current practice.

I have attached some specific comments on ACS's submission.

cc: Kevin Garrahan
Wayne Hartwick

000103

Comments on Appendix A of Position Paper
on Proposed Modifications to Soil Clean-Up Levels
American Chemical Services Site, Griffith, Indiana

by

Karen A. Hammerstrom
USEPA/ORD/OHEA
Exposure Assessment Group
March 18, 1993

The document, *Dermal Exposure Assessment: Principles and Applications* (USEPA, 1992) is not intended to be a guidance document that supersedes *Risk Assessment Guidance for Superfund* (RAGS). USEPA (1992) is currently a review draft. EPA's Science Advisory Board (SAB) has recently completed a review. USEPA (1992) is intended to be a compilation of the latest scientific information available on percutaneous absorption of chemicals from soil and water and to serve as a support document for Superfund risk assessors. Recommendations for absorption factors were provided only where supported by data. In Section 6 of USEPA (1992), which reviews studies of dermal absorption from soil, only three specific absorption factors were recommended -- for 2,3,7,8-TCDD, 3,3',4,4'-tetrachlorobiphenyl (TCB), and cadmium. In addition, USEPA (1992) recommends that the highest values recommended for TCDD and TCB be used for all dioxins and furans and for all PCBs, respectively. No other recommendations have been made and it is the assumption of ORD that the Regional Offices and OERR are continuing to assess the existing data and determine default values as was done in the past.

In general, EAG recommends using absorption factors of 3% for all dioxins and furans and 6% for all PCBs. The only time lower values could conceivably be used is for the specific chemicals tested (2,3,7,8-TCDD and 3,3',4,4'-TCB) when the soil is known to have a very high organic carbon content (values of 0.1% for 2,3,7,8-TCDD and 0.6% for 3,3',4,4'-TCB are based on soil with an organic carbon content of about 1%).

The default values used in the baseline risk assessment seem reasonable. I have been studying all the data on percutaneous absorption of arsenic, cadmium, CrIII, CrVI, inorganic and organic mercury, and nickel from all media. There are few studies and most of the studies are not very relevant to the exposure scenarios at Superfund sites. But taken as a whole (excluding organic mercury which appears to behave differently from the inorganics), the studies support a default value of 1% but not much less. The default value of 30% for the SVOCs is also very reasonable. In an early draft of USEPA (1992), a default value of 50% was suggested for SVOCs. However, some members of our work group felt that absorption could be greater than 50% under some circumstances, and the default recommendation was dropped. Certainly, 30% absorption is theoretically possible when soil loadings are low. With respect to VOCs, there are even fewer data to support default values. Studies of absorption of VOCs from water indicate that skin is quite penetrable to some of

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these chemicals. Studies of absorption of soil-applied benzene, toluene, xylene, and ethylbenzene under occlusion discussed in USEPA (1992) support the 30% default value. The question is whether VOCs will evaporate before they can be absorbed when contacted in the environment. We haven't yet addressed this issue. The Kissel study on hexadecane is suggestive. However, we have not studied the data. The discussion in USEPA (1992) is based on telephone discussions and a poster at a conference. We will probably have a more extensive discussion of the Kissel data in the post-SAB review version of USEPA (1992), but I seriously doubt that we will recommend a low default value for all VOCs based on a study of one chemical.

USEPA (1992) specifically cautions against adjustment of absorption data to shorter time periods based on assumptions of linearity. In the available experiments, exposure periods are usually 24 hours or longer. Shu et al. (1988) studied absorption of 2,3,7,8-TCDD in a soil matrix in vivo at 4 and 24 hours in hairless and haired rats. Their data indicate that about 63% of the amount of TCDD absorbed in 24 hours was absorbed in 4 hours. Mobil Oil also studied absorption in vivo of a neat dose of 10 ng/cm² of TCDD in rats (unpublished data). In the first group of rats, sacrificed 8 hours after application of the TCDD, an average of 33.3% of the applied dose was found in tissues, excreta, and in the skin site after removal of unabsorbed residual TCDD. In the second group of subjects, sacrificed 96 hours after application, an average of 77.6% of the applied dose was found in excreta, tissues, and skin site after removal of unabsorbed TCDD. Thus, the amount absorbed in vivo after 8 hours was 42% of the amount absorbed after 96 hours of exposure.

An analysis of absorption of chemicals from water suggests that the rate at which a chemical penetrates the stratum corneum in the period before steady state is often greater than the rate of penetration during steady state (USEPA, 1992). EAG has decided that it would be inappropriate to use a linear scaling procedure to adjust absorption rates to time periods shorter than the exposure durations used in experiments. This issue was raised at EPA's dermal exposure work shop in April 1991. All those who commented on the issue had the opinion that existing experimental data did not support such a linear adjustment.

Another concern in drawing too many conclusions from too few data is that the soil loadings used in the experiments are much higher than those used in the environmental scenarios. Since the absorption factors are reported as percents absorbed, they are by definition dose dependent. One might expect the percentage of applied dose absorbed to increase as the applied dose decreases.

As an example of the effect of the soil adherence value on the estimate of absorbed dose, consider that while USEPA (1992) recommends soil adherence factors of 0.2 mg soil/cm² as a typical value and 1.0 mg/cm² as a high end value, the amounts of soil

used in the TCB experiments described in USEPA (1992) were approximately 10 mg/cm² for experiments involving rats and rat skin and approximately 6 mg/cm² for experiments involving human skin. For a TCB concentration of 1,000 ppm, assuming that 6% of the applied dose is absorbed, the amounts absorbed would be 0.012 µg TCB/cm² from 0.2 mg soil/cm² and 0.06 µg TCB/cm² from 1.0 mg soil/cm², as compared to absorption of 0.36 µg/cm² from 6 mg soil/cm². Another way of evaluating these data that is much more conservative than the USEPA (1992) approach is to assume that the amount rather than the percentage of TCB absorbed is constant regardless of dose; that is, that 0.36 µg/cm² of TCB would be absorbed over 24 hours regardless of the initial dose. If this assumption were true, 100% of a dose of 0.2 µg TCB/cm² (1,000 ppm TCB applied in 0.2 mg soil/cm²) and 36% of a dose of 1.0 µg TCB/cm² (1,000 ppm TCB applied in 1.0 mg soil/cm²) would be absorbed in 24 hours. The same argument may be made for the TCDD and cadmium data.

Generally, 1 mg/cm² is used as a soil adherence factor in Superfund assessment, rather than 0.2 mg/cm², as more representative of a high-end value.

A comment was made that rat skin is three times more permeable than human skin. Actually, relative permeability is chemical specific. For some chemicals, human skin is the more permeable. Where no data are available on relative permeabilities, USEPA (1992) recommends using animal data without adjustment to estimate absorption factors.