Appendix B. Fact Sheets Containing a Summary of Data Used to Identify a Toxicity Value (Acute Oral Reference Dose) Used in the Calculation of Soil Cleanup Objectives Based on the Potential for Acute Toxicity In Children Who May Ingest A Large Amount of Soil.

Chemical Name: Barium
Effects: Gastrointestinal irritation (human)
Provisional Acute Reference Dose: 0.3 mg/kg

New York State Department of Health
Summary of Information Used to Identify an Acute Reference Dose

The ingestion of concentrated solutions of soluble barium salts (barium chloride or carbonate) reported causes gastrointestinal disturbances, including gastric pain, vomiting, and diarrhea, as the initial symptoms in adult humans. Various reports (Calabrese et al., 1997; IPCS, 1990, 1991; FL DEP, 2004, Health Canada, 1990) cite 200 to 500 mg of barium/person as the dose range associated with gastrointestinal effects. These estimates correspond to approximately 3 to 7 mg/kg assuming an adult body weight of 70 kg.

Confidence in these dose estimates is low because data in support of the range of doses are minimal. Most sources cite Reeves (1979) in support of 200 – 500 mg. However, Reeves (1979) does not provide a description of the toxic effects seen at these doses nor does he provide any documentation for his estimates.

The lowest calculated dose (3 mg/kg) associated with gastrointestinal effects is selected as the acute dose for use in the analysis. An uncertainty factor of 10 was used to compensate for human variation in pharmacodynamics (i.e., sensitivity), and the use of an effect level for a mild, transient effect (i.e., LOEL). An additional uncertainty factor to compensate for human variation in pharmacokinetic differences was not applied because the gastrointestinal effects were likely the result of direct contact between the barium solution and cells lining the gastrointestinal tract. This minimizes the importance of pharmacokinetics. Thus, the barium provisional RfD_{acute} is 0.3 mg/kg (i.e., 3 mg/kg/10-fold uncertainty factor).

Barium References

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological Profile for Barium (Update). Atlanta, GA: US Public Health Service, US Department of Health and Human Services.

Calabrese EJ, Stanek EJ, James RC, and Roberts SM. 1997. Soil ingestion: A concern for acute toxicity in children. Environ Health Perspect. 105(12):1354-1358.

FL DEP (Florida Department of Environmental Protection). 2004. Draft Technical Report: Development of Cleanup Target Levels (CTLs) for Chapter 62-777, F.A.C. Prepared for the Division of Waste Management by HG Ochoa, B Gadagbui, JK Tolson, and SM Roberts, Center for Environmental & Human Toxicology, University of Florida, Gainesville, Florida.

IPCS (International Programme on Chemical Safety). 1990. Environmental Health Criteria 107 – Barium. Geneva, Switzerland: United Nations Environment Programme, International Labour Organization, and the World Health Organization

IPCS (International Programme on Chemical Safety). 1991. Health and Safety Guide No. 46 – Barium. Geneva, Switzerland: United Nations Environment Programme, International Labour Organization, and the World Health Organization

Health Canada. 1990. Guidelines for Canadian Drinking Water Quality. Technical Support Document for Barium. Ottawa, Ontario: Water Quality and Health Bureau, Safe Environments Programme.

Reeves, AL. 1979. Barium. In: Handbook on the Toxicology of Metals. L. Friberg, G.F. Nordberg and V.B. Vouk (eds.). Amsterdam: Elsevier/North Holland Biomedical Press. pp. 321-328.

Chemical Name: Cadmium
Effects: Gastrointestinal irritation (humans)
Provisional Acute Reference Dose: 0.007 mg/kg

New York State Department of Health
Summary of Information Used to Identify an Acute Reference Dose

The ingestion of concentrated solutions of cadmium causes severe irritation to the gastrointestinal epithelium (ATSDR, 1999). Common symptoms in humans following ingestion of food or beverages containing high concentrations of cadmium include nausea, vomiting, salivation, abdominal pain, cramps, and diarrhea. In mild cases, recovery was rapid and complete. Although exact doses are uncertain, gastrointestinal symptoms have been observed in children consuming soft drinks with cadmium levels at 16 mg/L (Nordberg et al., 1973), and adults and children consuming liquids/foods containing 300 mg/L (lemonade), 67 mg/L (fruit punch), 160 mg/L (tea), and 13 – 15 mg/L (popsicles) (Frant and Kleeman, 1941).

ATSDR (1999) estimated a dose that would cause nausea and vomiting was about 0.07 mg/kg and apparently based their estimate on data (16 mg/L x 0.15 L consumer per person) from Nordberg et al. (1973), and the assumption of a body weight of 35 kg for a child.

NAS/NAE (1972) estimated that doses of 1.3 – 3 mg/person caused gastrointestinal effects in children who ingested contaminated popsicles. They used Frant and Kleeman (1941) data on the concentration found in the popsicles (13 – 15 mg/L), but did not provide documentation on how they calculated their dose estimates. Their estimated doses correspond to 0.04 mg/kg – 0.09 mg/kg, assuming a body weight of 35 kg for a child.

Lauwerys (1979) states that the no-effect level for gastrointestinal effects in man from a single oral dose is estimated at 3 mg, which corresponds to 0.04 mg/kg assuming a body weight of 70 kg for an adult. However, documentation in support of this estimate was not provided

Confidence in these dose estimates is low because the reports only provide data on the level of cadmium in the liquids/food. Data on body weight and amounts of contaminated liquid/food

consumed were not reported (Frant and Kleenman, 1941) or unavailable (Nordberg et al., 1973). ATSDR (1999) apparently obtained information on the amounts of contaminated food ingested, and thus, the only assumption necessary to estimate dose was that of a 35-kg body weight for a child.

ATSDR (1999) provided the most documentation in support of dose (0.07 mg/kg) associated with gastrointestinal effects. It is the value selected for use in the analysis. It is midway between the lowest and highest dose estimates (0.04 to 0.09 mg/kg) associated with gastrointestinal effects. An uncertainty factor of 10 was used to compensate for human variation in pharmacodynamics (i.e., sensitivity), and the use of an effect level for a mild, transient effect (i.e., LOEL). An additional uncertainty factor to compensate for human variation in pharmacokinetic differences was not applied because the gastrointestinal effects were likely the result of direct contact between the cadmium solution and cells lining the gastrointestinal tract. This minimizes the importance of pharmacokinetics. Thus, the cadmium provisional RfD_{acute} is 0.007 mg/kg (0.07 mg/kg/10-fold uncertainty factor).

Cadmium References

ATSDR (Agency for Toxic Substances and Disease Registry). 1999. Toxicological Profile for Cadmium (Update). Atlanta, GA: US Public Health Service, US Department of Health and Human Services.

NAS/NAE (National Academy of Sciences and National Academy of Engineering). 1972. Water Quality Criteria, 1972. A Report of the Committee on Water Quality Criteria. Washington, DC: US Government Printing Office. 593 pp.

Frant S, and Kleeman I. 1941. Cadmium 'food poisoning'. J Am Med Assoc. 117:86-89.

Lauwerys R. 1979. Cadmium in man. In: The Chemistry, Biochemistry and Biology of Cadmium. Webb M, ed. NY,NY: Elsevier/North Holland Biomedical Press. pp. 433-455.

Nordberg GF, Slorach S, and Stenstrom T. 1973. Kadmiumforgiftning orsakad av kalidrycksoutumat. Lakartidningen 70:601 (as cited in ATSDR, 1999).

Chemical Name: Copper
Effects: Gastrointestinal irritation (humans)
Provisional Acute Reference Dose: 0.2 mg/kg

New York State Department of Health
Summary of Information Used to Identify an Acute Reference Dose

The ingestion of drinking water or beverages with elevated copper concentrations causes gastrointestinal effects, including nausea, vomiting, diarrhea, and abdominal pain (NRC, 2000; Araya et al., 2001, 2003; Olivares et al, 2001; Pizarro et al., 1999). Data from control experimental studies with human volunteers designed to evaluate the effects of acute copper exposure from drinking water were considered the most appropriate for use in the analysis.

Sixty healthy, adult women were randomly assigned to receive copper at four concentrations in their drinking water (Pizarro et al., 1999). Each group (n = 15) received tap water with no added copper, 1, 3, and 5 mg Cu/l of added copper sulfate for a 2-week study period, followed by 1 week of standard tap water. The subjects recorded their water consumption and gastrointestinal symptoms daily. A significant increase in gastrointestinal symptoms (nausea, abdominal pain, and vomiting) was reported among women consuming water containing 3 mg/L copper. Thus, the NOEL and LOEL were 1 mg/L and 3 mg/L, respectively. These concentrations correspond to doses of 0.027 mg/kg and 0.073 mg/kg/day, based on average daily intakes of copper in water (1.74 mg/day, and 4.68 mg/day, respectively) and average body weight (64 kg) of study participants.

Other studies focused on the induction of gastrointestinal effects in fasting subjects after the ingestion of 0.2 L of copper-contaminated water under controlled laboratory conditions. In one study (Olivares et al., 2001), the NOEL and the LOEL for complaints of nausea were 2 mg/L (0.4 mg/person) and 4 mg/L (0.8 mg/person), respectively, for copper dissolved in purified tap water. In follow-up studies of slightly different experimental design (Araya et al., 2001, 2003), the NOEL and LOEL for complaints of nausea and other gastrointestinal effects were 4 mg/L (0.8 mg/person) and 6 mg/L (1.2 mg/person,) respectively for copper dissolved in distilled or bottle spring water. In all studies, the effects were mild, short-lived, and occurred only once

shortly after consumption of the water. The doses 0.4, 0.8, and 1.2 mg/person correspond to doses of 0.0057, 0.011, and 0.017 mg/kg/day, respectively, assuming a body weight of 70 kg for an adult.

The NOEL for gastrointestinal effects from the Pizarro et al. (1999) study is substantially higher than the NOELs and LOELs from the other studies when expressed as a copper dose (mg/kg/day).

Study	Volume of Water Consumed (L/person)	mg/kg/day	
		NOEL	LOEL
Pizarro et al. (1999)	1.7	0.027	0.073
Olivares et al. (2001)	0.2	0.0057	0.011
Araya et al. (2001, 2003)	0.2	0.011	0.017

However, the variation in NOELs is reduced when they are expressed as a concentration of copper in water (mg/L). These minor differences are likely dependent on the different populations and experimental designs.

Study	Volume of Water Consumed (L/person)	mg/L	
		NOEL	LOEL
Pizarro et al. (1999)	1.7	1	3
Olivares et al. (2001)	0.2	2	4
Araya et al. (2001, 2003)	0.2	4	6

Collectively, these data suggest that water concentration (mg/L) is a more accurate predictor of the likelihood of acute gastrointestinal effects from the ingestion of copper-containing water than is the daily dose (mg/kg). In fact, the NRC (2000) considered drinking-water concentration to be the appropriate dose meter for evaluating drinking-water standards with respect to acute gastrointestinal effects of copper. It is likely that copper-induce gastric irritation is a receptor-mediated effect of copper ion on the lining of the stomach, (NRC, 2000). If so, copper concentration of the ingested liquid, rather than the amount of copper ingested, might be a better predictor of toxicity. However, is also possible that the likelihood of gastrointestinal effects also depends, to a lesser extent, on the interaction between the concentration and the volume consumed. Additional work is needed to establish the relationship between concentration, volume consumed, and gastrointestinal effects (NRC, 2000).

The highest NOEL than is lower than any LOEL is 2 mg/L and it is identified as the acute NOEL for copper in water. This concentration is similar to the US EPA (2004) and NYS DOH (2001) action level for copper in water (1.3 mg/L) which is based on weak data on acute gastrointestinal effects (see Copper: Oral Non-Cancer Toxicity Value Documentation, Appendix A). It is equal to the World Health Organization's provisional drinking water guideline for copper of 2 mg/L. Moreover, Olivares et al (1998) arranged for healthy infants to receive drinking water with 2 mg/L of copper from 3 to 12 months of age, and reported that neither acute nor chronic adverse effects were detected in infants during the first year of life. In view of these data and those that show copper is an essential nutrient (IOM, 2001; NRC, 2000), an uncertainty factor of 1 is used to identify a provisional RfD_{acute} for copper in water. An uncertainty factor of 1 was also used by the US Institute of Medicine to derive a copper chronic reference dose from a human NOEL (IOM, 2001) (see fact sheet on Copper: Oral Non-Cancer Toxicity Value Documentation in Appendix A).

An estimate of daily dose, expressed as mg/kg/day, at the NOEL concentration is necessary to derive a soil cleanup objective based on acute toxicity data. The data from the acute studies are useful for identifying 2 mg/L as the NOEL for acute gastrointestinal effects. However, the greater inconsistency in the NOEL and LOEL estimates (mg/kg) from the studies suggest they are not useful for the identification of a NOEL expressed as a daily dose. Consequently, the daily dose expected at 2 mg/L in drinking water was used instead. This concentration is equal to RfD_{acute} and the WHO drinking water guideline. Gastrointestinal effects at the guideline are not expected. Assuming a 10-kg child drinks 1 liter of water day, the dose at 2 mg/L is 0.2 mg/kg, and it is the value used in the analysis.

Copper References

Araya M, McGoldrick MC, Klevay LM, et al. 2001. Determination of an acute no-observed-adverse-effect level (NOAEL) for copper in water. Regul Toxicol Pharmacol. 34(2):137-145.

Araya M, Chen B, Klevay LM, et al. 2003. Confirmation of an acute no-observed-adverse-effect and low-observed-adverse-effect level for copper in bottled drinking water in a multi-site international study. Regul Toxicol Pharmacol. 38(3):389-399.

IOM (Institute of Medicine). 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press.

NYS DOH (New York State Department of Health). 2001. 10 NYCRR (New York State Codes, Rules and Regulations). Part 5, Subpart 5-1. Public Water Systems. Albany, NY: New York State Department of Health.

NRC (National Research Council). 2000. Copper in Drinking Water. Washington, DC: National Academy Press.

Olivares M, Araya M, Pizarro F, Uauy R. 2001. Nausea threshold in apparently healthy individuals who drink fluids containing graded concentrations of copper. Regul Toxicol Pharmacol. 33(3):271-275.

Olivares M, Pizarro F, Speisky H, et al. 1998. Copper in infant nutrition: safety of World Health Organization provisional guideline value for copper content of drinking water. J Pediatr Gastroenterol Nutr. 26:251-257.

Pizarro F, Olivares M, Uauy R, et al. 1999. Acute gastrointestinal effects of graded levels of copper in drinking water. Environ Health Perspect. 107(2):117-121.

US EPA (US Environmental Protection Agency). 2004. 2004 Edition of the Drinking Water Standards and Health Advisories. EPA 822-R-04-005. Washington, DC: Office of Water.

WHO (World Health Organization). 1996. Guidelines for Drinking-Water Quality. Second Edition. Volume 2. Health Criteria and Other Supporting Information. Geneva, Switzerland: World Health Organization.

Chemical Name: Cyanide
Effects: None observed (animals)
Provisional Acute Reference Dose: Not derived, chronic reference dose of 0.02 mg/kg used instead

New York State Department of Health
Summary of Information Used to Identify an Acute Reference Dose

Reliable data on the doses associated with non-fatal toxic effects in humans exposed to cyanide are limited (ATSDR, 1997, MA DEP, 1992). A variety of effects (shortness of breath, breakup of muscle fibers, increased liver serum enzymes) were seen in a man who intentionally ingested and survived a dose of 40 mg of cyanide as potassium cyanide (Saincher et al., 1994). The amount ingested corresponds to a dose of 0.57 mg/kg of cyanide assuming a body weight of 70 kg. However, Gettler and Baine (1938) estimated the minimum lethal human dose is 0.58 mg/kg, and based their estimate on four case studies.

Confidence in both dose estimates is high. Saincher et al. (1994) estimated the dose from the information provided by the patient and his body weight. Its use in the analysis is precluded because it is similar to the fatal dose reported by Gettler and Baine (1938), and the patient received supportive care in the emergency room. Gettler and Baine (1938) estimated lethal doses from measurements of the amounts of cyanide in the brain, liver, and gastrointestinal tract (a validated method) and each victim's body weight. However, only four people were included in the study. Moreover, the use of lethality data in deriving reference doses is inconsistent with the general guidelines for the derivation of chronic reference doses (ATSDR, 1996; US EPA, 2002). Thus, these data are not used in the analysis.

An alternative dose for use in the analysis is the chronic reference dose (0.02 mg/kg/day) for cyanide (see fact sheet on the Oral Non-Cancer Toxicity Value Documentation for Cyanide in Appendix A). The chronic reference dose was based on a 2-year dietary study in male and female rats that did not observe any effects at any dose level. The chronic reference dose is

about 30-times lower than the lowest lethal dose (0.58 mg/kg) identified in the acute data evaluation. It is selected for use in the analysis.

Cyanide References

ATSDR (Agency for Toxic Substances and Disease Registry). 1996. Minimal Risk Levels for Priority Substances and Guidance for Derivation; Republication. Fed. Register. 61:33511-33515. (June 27).

ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Cyanide. Atlanta, GA: US Public Health Service, US Department of Health and Human Services.

Gettler AO, and Baine JO. 1938. The toxicology of cyanide. Am J Med Sci. 195:182-198.

MA DEP (Massachusetts Department of Environmental Protection). 1992. Background Documentation for the Development of an "Available Cyanide" Benchmark Concentration. Boston, MA: Office of Research and Standards. (available on-line at http://www.mass.gov/dep/ors/files/cn_soil.htm)

Saincher A, Swirsky N, and Tenenbein M. 1994. Cyanide overdose: Survival with fatal blood concentration without antidotal therapy. J Emerg Med. 12(4):555-557.

US EPA (US Environmental Protection Agency). 2002. A Review of the Reference Dose and Reference Concentration Process. Final Report. EPA/630/P-02/002F. Washington, DC: Risk Assessment Forum.

Chemical Name: Nickel
Effects: Gastrointestinal (humans)
Provisional Acute Reference Dose: 0.23 mg/kg

New York State Department of Health
Summary of Information Used to Identify an Acute Reference Dose

A few human case reports have shown that ingestion of concentrated solutions of soluble nickel compounds can cause gastrointestinal effects (IOM, 2001; IPCS, 1991; Sunderman et al., 1988). Sunderman et al. (1988) investigated an accidental poisoning of 32 individuals who drank contaminated water from a fountain. The water contained 16,300 mg nickel/L as nickel sulfate and nickel chloride (two highly soluble nickel compounds) and some boric acid (68 mg/L). Twenty workers rapidly developed symptoms. The most common symptoms were nausea and abdominal cramps or discomfort. Symptoms typically lasted a few hours, but persisted for 1-2 days in 7 cases. Ten workers were hospitalized. The nickel doses in workers with symptoms were estimated to range from 500 to 2,500 mg per person. These doses correspond to 7 mg/kg to 36 mg/kg, respectively, assuming a body weight of 70 kg for an adult.

Confidence in dose estimates is moderate because they were based on approximation of the amount of water consumed ("…workers who developed symptoms evidently had ingested 0.5 to 1.5 liters of water….") and measured concentrations of nickel in the water from the fountain. It is likely that the measured values were representative of the water that the workers consumed because of the shortness of the contamination episode (evening shift) and the promptness of the measurements (night shift). The uncertainties introduced by use of assumed body weight is likely to be minimal. Sunderman et al. (1988) indicated that the intake of 20 - 200 mg boric acid probably did not contribute to the observed effects because the effects of boric acid are generally observed after ingestion of $\geq$ 4,000 mg by adults.

The dose (7 mg/kg) is selected as the value for use in the analysis. An uncertainty factor of 30 was used to compensate for human variation in pharmacodynamics (i.e., sensitivity), and the use of an effect level (i.e., a LOEL) for gastrointestinal effects that lasted, at least in some cases, more than a few hours. An additional uncertainty factor to compensate for human variation in

pharmacokinetic differences was not applied because the gastrointestinal effects were likely the result of direct contact between the nickel solution and cells lining the gastrointestinal tract. This minimizes the importance of pharmacokinetics. Thus, the nickel provisional RfD_{acute} is 0.23 mg/kg (7 mg/kg/30-fold uncertainty factor).

Nickel References

ATSDR (Agency for Toxic Substances and Disease Registry). 2003. Toxicological Profile for Nickel. Update. Draft for Public Comment. Atlanta, GA: US Public Health Service, US Department of Health and Human Services.

IPCS (International Programme on Chemical Safety). 1991. Environmental Health Criteria 108 – Nickel. Geneva, Switzerland: United Nations Environment Programme, International Labour Organization, and the World Health Organization

IOM (Institute of Medicine). 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press.

Sunderman FW, Dingle B, Hopfer SM, and Swift T. 1988. Acute nickel toxicity in electroplating workers whom accidentally ingested a solution of nickel sulfate and nickel chloride. Am. J. Ind. Med. 14:257-266.

Chemical Name: Pentachlorophenol
Effects: Developmental (rats)
Provisional Acute Reference Dose: 0.005 mg/kg/day

New York State Department of Health
Summary of Information Used to Identify an Acute Reference Dose

A comprehensive search did not find any information on the oral pentachlorophenol doses associated with non-lethal toxic effects in humans (ATSDR, 2001; NRC, 1986; IPCS, 1987; Proudfoot, 2003), thus, animal data are used in the analysis. ATSDR (2001) derived an oral acute minimal risk level based on the results of a developmental toxicity study (Schwetz et al., 1974). ATSDR (2001) identified a LOEL of 5 mg/kg/day for delayed ossification of the skull in rat pups when the dams were given pure pentachlorophenol by corn oil gavage on gestation days 6 through 15.

Assuming the fetus is a reasonable surrogate for a young child, the LOEL of 5 mg/kg is selected as the value for use in the analysis. An uncertainty factor of 1,000 is commonly recommended when deriving a reference dose from a LOEL from an animal study (US EPA, 2002). This uncertainty factor compensates for human variation, interspecies differences between animals and humans, and the use of a LOEL instead of a NOEL. Thus, the pentachlorophenol provisional RfD_{acute} is 0.005 mg/kg (5 mg/kg/1,000-fold uncertainty factor).

Pentachlorophenol References

ATSDR (Agency for Toxic Substances and Disease Registry). 2001. Toxicological Profile for Pentachlorophenol. Atlanta, GA: US Public Health Service, US Department of Health and Human Services.

NRC (National Research Council). 1986. Drinking Water and Health. Volume 6. Washington, DC: National Academy Press.

Proudfoot AT. 2003. Pentachlorophenol poisoning. Toxicol Rev. 22(1):3-11.

IPCS (International Programme on Chemical Safety). 1987. Environmental Health Criteria 71 – Pentachlorophenol. Geneva, Switzerland: United Nations Environment Programme, International Labour Organization, and the World Health Organization

Schwetz BA, Keeler PA, and Gehring PJ. 1974. The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development. Toxicol Appl Pharmacol. 28:151-161.

US EPA (US Environmental Protection Agency). 2002. A Review of the Reference Dose and Reference Concentration Process. Final Report. EPA/630/P-02/002F. Washington, DC: Risk Assessment Forum.

Chemical Name: Phenol
Effects: Developmental (rats)
Provisional Acute Reference Dose: 0.6 mg/kg/day

New York State Department of Health
Summary of Information Used to Identify an Acute Reference Dose

The deliberate ingestion of large amounts of phenol can be fatal; the lowest dose lethal to humans had been estimated to be 140 mg/kg (US EPA, 1986). There are some data on oral doses associated with non-lethal effects.

In a retrospective study of 158 persons served by a public water supply contaminated by an accidental spillage of phenol, the incidences of mouth sores, burning mouth, dark urine, and diarrhea among 39 individuals in families living in homes with phenol levels >0.1 mg/L were significantly higher ($p < 0.0l$) than those among the unexposed control group of families containing 119 individuals (Baker et al. 1978). Data on symptoms were collected for 7 months after the spill, but symptoms among the exposed residents peaked during the 2 months after the spill. The estimated doses for 17 individuals from the exposed group who showed two of the four symptoms used to define a case (diarrhea, mouth sores, dark urine, and burning of the mouth) ranged from 10 to 240 mg/person/day. These doses correspond to 0.14 to 3.4 mg/kg/day assuming a body weight of 70 kg for an adult.

Confidence is the dose estimate is low for four reasons. (1) Dose estimates were based on recall of "water preference histories," but it is not clear exactly what data were collected. (2) Data on amounts of water consumed by each affected individual or on the water concentrations used to estimate doses were not provided, except to say that sampling data collected within 2 months after the spill were used. (3) The length of exposure for each individual was not reported, however, it was likely to be longer than 1 event or 1 day. (4) Although the uncertainties introduced by use of assumed body weight is likely to be minimal if only adults were affected, whether or not this was the case is uncertain because the individuals in affected "families" could have been children. Thus, the dose estimates were deemed inadequate for use in the analysis.

A retrospective review of phenol poisoning reported to a regional poison control center, Spiller et al; (1993) evaluated, when possible, the dose associated with oral-only exposures. 75% of the patients were under 5 years old. Based on the reported information on age, dose, and nature of effects, the smallest dose associated with any effects was 1.3 g, which corresponds to a dose of 98 mg/kg assuming a body weight of 13.3 for a 2.5-year old child (US EPA, 2002a).

Acute doses for use in the analysis also are provided by the results of developmental studies in female rats, which assessed both maternal and developmental effects. In these studies, the pregnant rats were given oral doses of phenol on gestation days 6 – 15, and then dams and pups were examined on gestation day 20. Both studies used gavage doses of phenol dissolved in water, one study identified the concentration as 90% phenol (US EPA, 2002b). In one study, the US EPA (2002b) identified 60 mg/kg as NOEL for decreases in maternal body weight. The NOEL for development effects was higher. In the second study, the US EPA (2002b) identified 60 mg/kg as the NOEL for decreases in fetal body weight. The NOEL for maternal effects was higher.

Assuming the fetus is a reasonable surrogate for a young child, the NOEL of 60 mg/kg for decreased in fetal body weight is selected as the value for use in the analysis. It is a reliable NOEL and is lower than the lowest acute dose associated with accidental poisonings in children. An uncertainty factors of 100 is commonly recommended when deriving a reference dose from a NOEL from an animal study (US EPA, 2002c). This uncertainty factor compensates for human variation and for interspecies differences between animals and humans. Thus, the phenol provisional RfD_{acute} is 0.6 mg/kg (60 mg/kg/100-fold uncertainty factor).

Phenol References

ATSDR (Agency for Toxic Substances and Disease Registry). 1998. Toxicological Profile for Phenol. Atlanta, GA: US Public Health Service, US Department of Health and Human Services.

Baker EL, Landrigan PJ, Bertozzi PE, et al. 1978. Phenol poisoning due to contaminated drinking water. Arch Environ Health. 33:89-94.

Spiller HA, Quadrani-Kushner DA, and Cleveland P. 1993. A five year evaluation of acute exposures to phenol disinfectant (26%). Clin Toxicol. 31:307-313.

US EPA (US Environmental Protection Agency). 1986. Summary Review of the Health Effects Associated with Phenol: Health Issue Assessment. EPA/600/8-86/003F. Washington, DC: Office of Health and Environmental Assessment.

US EPA (US Environmental Protection Agency). 2002a. Child-Specific Exposure Factors Handbook. Interim Report. EPA-600-P-00-002B. Washington, DC: National Center for Environmental Assessment.

US EPA (US Environmental Protection Agency). 2002b. Toxicological Review of Phenol (CAS No. 108-95-2) In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-02/006. Washington, DC: National Center of Environmental Assessment.

US EPA (US Environmental Protection Agency). 2002c. A Review of the Reference Dose and Reference Concentration Process. Final Report. EPA/630/P-02/002F. Washington, DC: Risk Assessment Forum.

Appendix C-1. Method for Deriving Soil Cleanup Objectives (SCOs) for Soil Contaminants Based on Toxicity Data for Irritant Contact Dermatitis (Non-Allergic Skin Irritation).

Introduction

The assessment of health risk effects from contaminated soils typically considers the potential systemic effects of inhalation, ingestion, and dermal exposures. However, skin itself can become damaged after direct contact with soils contaminated with chemicals. One of the most common forms of damage is irritant contact dermatitis (ICD), a localized non-allergic inflammatory response to chemical irritation.

For a typical residential exposure scenario, soil cleanup guidelines based on toxicity data for systemic effects and soil-associated oral, dermal, and inhalation exposures are thought to be lower than soil cleanup guidelines based on the toxicity data for ICD and direct soil contact with the skin. Other scenarios (industrial, for example) are likely to have higher cleanup guidelines than residential scenarios because the soil-associated oral, dermal, and inhalation exposures are lower than those for residential scenarios. Under these conditions, some soil cleanup guidelines based on ICD might be lower than soil cleanup guidelines based on systemic effects. Consequently, a method was developed to derive soil cleanup objectives based on toxicity data for ICD. This method was applied, when possible, to toxicity data for target contaminants or their surrogates. The resultant SCOs can be compared to SCOs based on the potential systemic effects of soil-associated exposures.

First, background information of skin structure, ICD, and methods to estimate dermal exposures from soil contaminants is presented. Then, the standard test methods for irritant dermatitis are discussed and the limited data derived from those studies are evaluated for their usefulness in deriving SCOs based on ICD. Next, SCOs for three target contaminants (phenol, nickel, and chromium) and a surrogate SCO for use with semi-volatile organic compounds that lack chemical-specific information on irritative potency are derived.

Structure of the Skin

The skin is composed of the epidermis and the dermis (Monteiro-Riviere, 1996; US EPA, 1992). The epidermis contains no nerves or blood vessels. The stratum corneum is the outermost layer

of the epidermis and is the major barrier to the absorption into the body of chemicals placed on the skin (Monteiro-Riviere, 1996). It is composed of dead, partially desiccated, and keratinized epidermal cells. Chemicals must get past the stratum corneum to cause inflammatory skin responses such as ICD. Below the stratum corneum is the viable epidermis, which contains keratinocytes (cells that make keratin), melanocytes (cells that make pigment), and Langerhan cells (cells of the immune system) as well as other specialized cells.

The dermis is below the epidermis. It is largely made up of collagen (fibrous or connective) tissue. The dermis makes up the bulk of the skin. Blood vessels, lymph vessels, nerves, sweat glands, oil glands, hair follicles, hair-erecting muscles, and other structures are found throughout the dermis.

Irritant Contact Dermatitis (ICD)

Irritant contact dermatitis is a non-immunologic, local inflammatory response at the site of contact following single, repeated, or continuous exposure to a chemical (English, 2004; Maibach and Patrick, 2001). The chemical could be a liquid, solid, or gas, or could be dissolved or suspended in a liquid or solid. It also could be dissolved in soil pore water or absorbed onto soil particles. ICD can develop after a short, heavy exposure or a repeated or prolonged, low exposure to an irritating substance. Several general classes of substances can cause ICD (Table 1). These substances damage the protective properties of the epidermis.

ICD is characterized by reddening of the skin (erythema), accumulation of fluids (edema) and various types of skin lesions (e.g., vesicles, pustules, and erosions) in more severe cases. People differ in their sensitivities to chemical irritants (Modjtahedi and Maibach, 2002; Modjtahedi et al., 2004, Robinson, 1999, 2001, 2002; Willis, 2002). The skin effects of ICD are similar to those of allergic contact dermatitis (ACD), which is a cell-mediated immune response to small molecular weight chemicals that contact and penetrate the skin.

Recommended Dose Metric

Two dose metrics (concentration expressed as ppm, and skin loading dose, expressed as mg contaminant/cm^2 skin) are used to describe dermal doses in studies in animals and humans (see reviews by Robinson et al., 2000; Upadhye and Maibach, 1992). Both metrics have been used in dose-response assessments of the risk of allergic contact dermatitis from dermal contact with soil contaminated with chromium (Felter and Dourson, 1997; Hazen and Stern, 1995; Horowitz and Finley, 1994; Nethercott et al., 1994). However, results from recent experiments on allergic contact dermatitis show that the amount of the chemical applied per area of skin, rather than the concentration of chemical applied to the skin, is a more accurate predictor of the severity of the response (Robinson et al., 2000). Recent assessments of the risk of allergic contact dermatitis from cosmetics also used skin loading dose in the dose-response assessments (Felter et al., 2002, 2003). Because both ICD and ACD are localized inflammatory responses in and near dermal cells in direct contact with the ions/molecules of the irritant chemicals, skin loading dose is used as the dose metric for dose-response assessments of ICD.

The Exposure Scenario

When human skin comes in contact with dry or moist soil, most of the soil falls off and only a percentage of the soil initially in contact with the skin remains on the skin. The amount that remains is described by a soil adherence factor and is expressed as mg soil per centimeter square of skin (mg soil/cm^2 skin). Multiplying the soil adherence factor by the contaminant soil concentration (for example, mg contaminant/mg soil) gives the skin loading dose (mg contaminant/cm^2 skin). The percentage of the skin loading dose that actually penetrates the stratum corneum is described by a dermal absorption fraction and is expressed as a unitless fraction. Once past the stratum corneum, the absorbed contaminant ions/molecules have the potential to cause local damage to the surrounding skin cells and to enter systemic circulation within the body. This appendix presents a method for deriving soil cleanup objectives (SCOs) for soil contaminants based on toxicity data for ICD. Section 5.2.2.3 (Exposure Assessment Parameters and Values – Dermal Pathway) presents the methods used to incorporate dermal absorption in the derivation of SCOs based on toxicity data for systemic health effects. The same parameter values for soil adherence factors and dermal absorption fractions, when possible,

are used in both assessments because the rate-limiting process in both ICD and absorption into the body is the passage of soil contaminant ions/molecules through the stratum corneum.

Priority Soil Contaminants

The priority soil contaminants for the Brownfield Cleanup Program include chemicals that are commonly found at contaminated sites. The list contains chemicals that are classified as volatile organic compounds (VOCs), semi-volatile organic compounds (SVOCs), other chemicals that are semi-volatile (pesticides), and inorganic chemicals. The likelihood of contaminant movement from soil onto and through the skin is dependent, on part, on the physical and chemical properties of the contaminant. These properties differ greatly among the VOCs, SVOCs, and inorganic chemicals, and they determine, at least in part, the likelihood that a chemical in each chemical class would actually penetrate the epidermis and initiate ICD.

SCOs based on the potential of volatile organic compounds (VOC) contained or trapped in soil to cause ICD were not derived because VOCs are more likely to move from soil to air rather than from soil to skin (US EPA, 2004), and thus, pose little risk of ICD. SCOs for semi-volatile organic compounds were derived when chemical-specific data on irritation and dermal absorption were available, or when there were chemical-specific data on irritation and surrogate data on dermal absorption. These decisions were based on the likelihood of penetration of the epidermis by SVOCs and the availability of a recommended dermal absorption fraction for some SVOCs and a surrogate absorption fraction applicable to all SVOCs (US EPA, 2004).

SCOs for metals were derived when chemical-specific data on irritation and dermal absorption were available. SCOs based on metal-specific data on irritation and surrogate data on dermal absorption were not derived because data are lacking to support a surrogate value applicable to all metals (US EPA, 2004). However, estimates of the dermal absorption fraction for two metals (cadmium and arsenic) are very low (0.03 and 0.001, US EPA, 2004). This increases the likelihood that a SCO based on a metal's toxicity data for ICD might be higher than SCOs based on its toxicity data for systemic effects and soil-associated ingestion or inhalation exposures.

Standard Tests for Irritant Contact Dermatitis (ICD)

Regulatory agencies have published guidelines for tests of ICD (Rush et al., 1995; US EPA, 1998a). The primary goal of these tests is the classification of the irritation potency of the undiluted chemical (e.g., non-irritant, slight irritant, moderate irritant, or severe irritant). The readily available data on each priority soil contaminant (summarized in Appendix C-2) provide limited and anecdotal information that suggests many of these contaminants are known or potential skin irritants. These data, however, do not provide any information on the irritant properties of the contaminants in soil. Nor do the data provide much information on dose-response relationships, which are needed to estimate a chemical's no-observed-effect level (NOEL) and/or lowest-observed-effect level (LOEL) for ICD. These NOEL and LOEL values are used in standard risk assessment methods for non-cancer effects (see Section 5.1.1, Toxicity Values for Systemic Health Effects). Because data from standardized tests of ICD do not provide quantitative dose-response data, these data are inadequate for use in the derivation of contaminant-specific SCOs based on ICD.

Standard Test for Allergic Contact Dermatitis (ACD)

ACD can be a serious disease. Consequently, regulatory agencies have developed guidelines for animal tests to screen chemicals for their potential to induce ACD in humans (Maibach and Patrick, 2001; Rush et al., 1995). Medical doctors and scientists have developed human tests to determine if people are allergic to specific chemicals (de Groot, 1994). The tests in animals are dermal sensitization tests and those in humans are patch tests. An agent that induces ACD is a sensitizer. These tests also provide data that might be used to estimate the agent's NOEL or LOEL for ICD.

ACD is a cell-mediated immune response, and is a form of delayed hypersensitivity (Maibach and Patrick, 2001). The response requires two distinct events. In the first phase, called induction, the chemical penetrates the stratum corneum into the viable epidermis, and stimulates the formation of allergen-activated memory T-cells in all parts of the body, including the skin. In the second phrase, called elicitation, re-exposure to the chemical reactivates the memory T-

cells and triggers an inflammatory response. The various animal testing protocols for allergic contact dermatitis typically contain an induction and an elicitation (also called challenge) exposure (Maibach and Patrick, 2001; Rush et al., 1995). In the induction exposure, the chemical is applied to the skin under conditions that are designed to maximize absorption into the body and the stimulation of a cell-mediated immune response. In challenge or elicitation exposure, the chemical is applied to the skin, which is then examined to determine if an allergic inflammatory response has developed at the contact site.

A confounding factor in the selection of a challenge dose is that the signs of ACD and ICD overlap greatly. It is difficult to separate mild cases of ACD from mild cases of ICD. Ideally, the challenge dose should minimize the likelihood of a false-negative conclusion (i.e., concluding incorrectly that a chemical is not a sensitizer because the challenge dose was not high enough to induce a cell-mediated response). The challenge dose must also minimize the likelihood of a false-positive conclusion (i.e., concluding incorrectly that a chemical is a sensitizer because the challenge dose was high enough to cause ICD). The challenge dose should be just above the threshold dose necessary for the induction of ACD but just below threshold dose for the induction of ICD. This is a difficult, perhaps impossible balance to achieve, but even if it is only approximated, the challenge dose used in animal tests can be considered a useful estimate of a chemical's NOEL for ICD.

Guinea pigs or mice are commonly used in dermal sensitization tests, and there are substantial differences in challenge dose protocol recommended for each species (Maibach and Patrick, 2001; Rush et al., 1995; US EPA, 1998b). In tests on guinea pigs, the challenge dose is applied to an area (abdomen or back) that has been treated to maximize absorption. This treatment might include shaving or clipping the hair, abrading the area to remove surface layers of dead epidermis, and treating the area with reagents to improve the absorption into the body. The area is then covered with a patch that is either occlusive (totally impermeable to moisture) or non-occlusive. In tests on mice, the challenge dose is applied (in solution or suspension) to the normal skin of an ear, which is left uncovered. In both protocols, the skin is examined for inflammatory responses, typically at 24 hours and/or 48 hours after application.

The exposure condition of the challenge dose in the mouse-ear test is more similar to that expected when humans contact contaminated soil is the exposure condition of the guinea-pig patch test. This supports using the challenge dose from a mouse-ear test to estimate NOELs for ICD. Consequently, the mouse ear test data are used in the development of SCOs.

The Mouse Ear Swelling Test (MEST)

Two mouse ear tests are used commonly as dermal sensitization tests: the mouse ear swelling test or MEST (Gad et al., 1986; Gad, 1994) and the mouse ear swelling assay or MESA (Thorne et al., 1991a,b). The tests are similar and data from both tests have been summarized (Table 3). However, the MEST is described below because it has been used to test more substances and has been recognized as a valid regulatory test for dermal sensitization (Maibach and Patrick, 2001; US EPA, 1998b).

MEST Protocol

The test protocol for the MEST has an induction and a challenge exposure (Gad et al., 1986; Maibach and Patrick, 2001). In the induction exposure, the abdominal area is treated to maximize the absorption of the chemicals into the body, and the test material is placed on the treated area once a day for three days. A one-week induction phrase allows time for the immune response to develop. The challenge dose of the test material (dissolved in a solvent) is applied to both sides of one ear of each mouse in the study, and the control ear of each mouse is treated identically only with solvent. The volume applied to each side of the ear is 10 microliters (10 mcL or 0.001 ml). At 24 and 48 hours after challenge, the inflammatory response is determined by comparing the swelling (thickness) of the treated ear with that of the untreated ear using a micrometer.

To maximize the reliability of the test, the challenge dose should be the highest dose than is not irritating to the ear (Gad et al., 1986; Gad, 1994). Thus, a range-finding study should be conducted for each chemical to determine its optimal challenge dose before the actual MEST. However, Gad et al. (1986) noted that the challenge dose could not be based only on irritation

criteria because such doses might pose a risk of systemic toxicity or be unachievable because of insolubility in the vehicle. Gad et al. (1986) reported that the challenge dose for 20 of 72 chemicals were based on irritation alone, 12 were based on irritation and a second criteria (toxicity or solubility) and the remaining were based on toxicity or solubility.

The medical database of the National Library of Medicine (PubMed) was searched for studies using the MEST or MESA, and the articles were reviewed to determine the challenge dose and criteria for choosing the dose (Table 2). Thus, the literature on the MEST/MESA contains estimates of NOELs for ICD for about 89 substances, including the 72 substances tested by Gad et al. (1986).

MEST Results (Target Contaminants)

Of the chemicals on the list of priority soil contaminants (Table 4), only six (acetone, benzene, methyl ethyl ketone, phenol, nickel as nickel sulfate, and chromium VI as potassium dichromate) were evaluated using the MEST/MESA (Table 2). These six chemicals were tested by Gad et al. (1986). Acetone, benzene, and methyl ethyl ketone were used by Gad et al. (1986) as solvents for the preparation of solutions of other chemicals to be tested in the MEST. In control studies, these solvents were tested at 100%. The use of ears treated with these solvents as negative controls indicates that Gad et al. (1986) did not consider them irritating under the experimental protocol. This conclusion is consistent with the high vapor pressure of these compounds and the likelihood that they evaporated from the mouse ear before they had penetrated the epidermis. Phenol, nickel, and chromium VI are discussed below.

Phenol

The challenge concentration for the phenol was 5% (approximately 50 mg of phenol/ml solution), based on irritant/toxicity criteria. This concentration was converted to an estimated NOEL (mg contaminant/cm^2 skin) for ICD using the following information.

- Total volume applied to the ear = 20 mcL, or 0.02 ml,

- Treated surface area of each mouse ear (both surfaces) = 2.8 cm^2 (approximately), based on data from Patrick et al. (1985) for a different strain of mice.
- 0.02 ml of solution/2.8 cm^2 of skin = 0.0071 ml of solution/cm^2 skin.
- 0.0071 ml solution/cm^2 of skin x 50 mg phenol/ml solution = 0.36 mg phenol/cm^2 of skin.

Thus, 0.36 mg/cm^2 of skin is the estimated mouse $NOEL_{ICD}$ for phenol.

Nickel

The challenge doses for nickel sulfate were 2 % (Cornacoff et al., 1988) or 10 % (Gad et al. (1986); the latter concentration was based on irritant/solubility criteria. The 2% and 10% solutions contain approximately 20 mg of nickel sulfate/ml solution and 100 mg of nickel sulfate/ml solution, respectively. The NOELs were estimated using the method used with the phenol data.

Cornacoff et al. (1988)

- Volume applied to mouse ear: 0.025 ml
- 0.025 ml of solution/2.8 cm^2 of skin = 0.0089 ml of solution/cm^2 skin.
- 0.0089 ml solution/cm^2 of skin x 20 mg nickel sulfate/ml solution = 0.18 mg/cm^2 of skin.

Gad et al. (1986)

- Volume applied to mouse ear: 0.020 ml
- 0.02 ml of solution/2.8 cm^2 of skin = 0.0071 ml of solution/cm^2 skin.
- 0.0071 ml solution/cm^2 of skin x 100 mg nickel sulfate/ml solution = 0.71 mg/cm^2 of skin.

However, nickel sulfate ($NiSO_4$) is approximately 38% nickel. Thus, the skin loading doses expressed as nickel are 0.068 mg/cm^2 of skin (0.38 x 0.18 mg/cm^2 of skin) and 0.27 mg/cm^2 of skin (0.38 x 0.71 mg/cm^2 of skin), respectively. These are the estimates of the mouse $NOEL_{ICD}$ for nickel.

Chromium VI

The challenge dose for potassium dichromate was 2 % (20 mg of potassium dichromate/ml solution), based on irritation (Gad et al., 1986) (Table 2).

- Volume applied to mouse ear: 0.020 ml
- 0.02 ml of solution/2.8 cm^2 of skin = 0.0071 ml of solution/cm^2 skin.
- 0.0071 ml solution/cm^2 of skin x 20 mg potassium dichromate/ml solution = 0.14 mg/cm^2 of skin.

However, potassium dichromate ($K_2Cr_2O_7$) is approximately 35% chromium. Thus, the skin loading doses expressed as chromium is 0.049 mg/cm^2 of skin (0.35 x 0.14 mg/cm^2 of skin). Thus, 0.049 mg/cm^2 of skin is the estimated mouse $NOEL_{ICD}$ for chromium

MEST Results (Chemicals Not On the List of Target Contaminants)

Chemical-specific data to estimate target contaminant NOELs for ICD (except for phenol, nickel, and chromium VI) were not found. Thus, the literature on the MEST/MESA was examined to determine if some other chemicals could be surrogates for those target contaminants that are SVOCs and do not have chemical-specific ICD data.-

The MEST/MESA literature provides data to estimate mouse NOELs for ICD for 89 chemicals (Table 2). Gad et al. (1986) tested the largest number of chemicals, including organic and inorganic industrial chemicals from a variety of chemical classes. Many of the other chemicals were tested because they were known or potential irritants. Others were tested to establish the validity of the MEST/MESA to identify sensitizers of differing potency.

The lowest challenge skin loading dose used by Gad et al. (1986) was 0.0036 mg/cm^2 skin, and it was used for croton oil (Table 3). However, croton oil is not an industrial chemical. It was most likely used as a positive control because it is a standard and potent irritant in pharmacological

testing (Blazso and Gabor, 1995; Clementi et al., 1994; Junior et al. 2003; Katayama et al., 2001). The lowest skin loading dose used by other groups was 0.00014 mg/cm^2 skin. This was used for anthralin (dithranol), a prescription-only topical medication (and skin irritant) for the treatment of psoriasis that also may stimulate hair growth (Medline Plus, 2005). Neither of these chemicals is a reasonable surrogate for contaminants typically found at Brownfield sites. Thus, they were not selected as surrogates for SVOC contaminants.

Inspection of the cumulative frequency curve (Figure 1) for mouse NOELs (mg/cm^2 skin) shows that a skin loading dose of about 0.04 mg/cm^2 skin is lower than about 85% of the values. More importantly some of the chemicals with a dose of $\leq$ 0.04 mg/cm^2 skin are industrial organic chemicals. Although these chemicals are all recognized as highly reactive chemicals and potent irritants (Table 4), and may not be persistent in soil, the value of 0.04 mg/cm^2 skin is selected as a surrogate mouse NOEL for each target contaminant that is a SVOC, including pesticides.

Human Patch Tests for Allergic Contact Dermatitis

Another potential source of data for estimating human NOELs for ICD are the concentrations recommended for use in a human patch test, which is a standardized protocol for determining whether a person is sensitized (i.e., allergic) to a specific chemical. Human patch tests only contain a challenge exposure because the purpose of the test is to determine if the person has already been sensitized to the chemical by prior exposures. In the challenge phase, the suspected allergen is dissolved in a suitable vehicle, applied to the skin, covered with an occlusive tape or patch. After a few days (typically at 2 – 4 days), the treated area is examined to determine if ACD has developed. The concentration of test substance used in the patch test for ACD is critically important in order to obtain results that can be reliably interpreted, thus, minimizing the number of false negatives or false positives (see previous discussion). Thus, the concentration recommended for use in patch testing of a chemical could be considered a crude estimate of the human NOEL for ICD for that chemical under the conditions of the patch test.

Many handbooks make recommendations for patch test concentrations (Adams, 1983; de Groot, 1994; Fisher, 1983). For example, de Groot (1994) has compiled recommended test

concentrations for about 3,700 chemicals, including some of the priority soil contaminants (Table 4). These concentrations were not converted to skin loading dose to estimate human NOELs for ICD because they cannot be accurately or readily converted to skin loading doses. Robinson et al. (2000) reported a six-fold difference in dose per unit area (i.e., mcg/cm^2) when the recommended volume for each of four different commercially available patch types was used. This difference is also present in the skin loading doses estimated from the patch test concentrations in Table 4. Thus, the patch test data were not used to estimate human NOELs for ICD.

Other information supports this decision. Hjorth (1987) has noted that the recommended concentrations may be too low because they have not been based on a sufficient number of sensitive patients. In addition, the condition of the patch test, particularly the use of an occlusive patch and a 2- to 4-day period of constant contact, is a much more severe exposure challenge that would be expected from contaminated soil.

Thus, the following mouse NOEL for ICD ($NOEL_{ICD}$) for contaminants applied to the skin in solution were identified.

Chemical	**Estimate of Mouse $NOEL_{ICD}$ (mg/cm^2 skin)***
phenol	0.36
nickel as nickel sulfate	0.068 and 0.27
chromium VI as potassium dichromate	0.049
SVOC surrogate	0.04

* Chemical applied in solution to ear of mouse.

Method for the Derivation of Soil Cleanup Objectives Based on Toxicity Data for Irritant Contact Dermatitis

Phenol

Estimation of Skin Reference Dose for a Phenol Solution

The available data support the identification of 0.36 mg/cm^2 skin as a mouse $NOEL_{ICD}$ for phenol. Historically, dose-response assessments based on the systemic non-cancer effects of chemicals use an uncertainty factor to compensate for interspecies differences between animals and humans. The magnitude of this uncertainty factor is usually 3 or 10 and it is applied to a NOEL (or its equivalent) that has been identified in animal studies (US EPA, 2002). Experimental data on a wide variety of substances support the use of an uncertainty factor of 10 for systemic non-cancer effects when chemical-specific data on species differences are not available (US EPA, 2002). However, experimental data to support the use, or if used, the magnitude of an interspecies uncertainty factor for use with a NOEL based on ICD are limited at best (Felter et al., 2002). Calabrese (1983) reported on the relative irritancy of seven chemicals in mice and humans. He noted that three chemicals were similarly irritating to humans and mice, three were more irritating to mice than humans, and one was less irritating in mice than humans. These limited and qualitative data suggest that mouse skin may be more sensitive than human skin to the irritant properties of chemicals.

The human patch test database is a second source of information that might provide useful information on the relative dermal sensitivities of mice and humans. As previously discussed, the recommended human patch test concentration for a chemical is a crude estimate of its $NOEL_{ICD}$. It cannot be accurately converted into a more accurate estimate of the human $NOEL_{ICD}$ (mg/cm^2 skin) because skin loading dose varies with patch type. However, the range of skin loading doses that might be achieved in patch tests using the recommended concentration and standard patch types can be determined. A comparison of human and mouse NOELs for the same chemicals might provide some insight into the relative sensitivities of mice and humans to the irritant properties of chemicals.

Table 5 contains estimates of the mouse NOELs (MEST) and human NOELs (patch test) for 18 chemicals. All estimates are expressed as skin loading doses (mg/cm^2 skin). Human estimates were based on the use of a Finn Chamber and a Hilltop Chamber. The Finn Chamber gives the lowest skin loading dose and the Hilltop Chamber gives the highest skin loading dose of four commonly used patch test systems (Robinson et al., 2000).

When the Finn-Chamber dose estimates are used, the geometric mean of the ratios (Mouse NOEL/Human NOEL) is 1.8 and 11 of the 18 ratios are above 1.2 (Table 5). This suggests humans are more sensitive than are mice. When the Hilltop-Chamber dose estimates are used, however, the geometric mean of the ratios is 0.30. In addition, only 1 of 18 ratios is above 1.2 and 16 of 18 ratios are less than 0.80 (Table 5). This suggests humans are less sensitive than are mice (Table 5). When both sets of ratios are combined, the geometric mean is 0.73, which indicates than humans were less sensitive to the irritating properties of these chemicals than were mice. Moreover, 50% of the ratios indicate human are less sensitive than mice (ratios < 0.8), 14% of the ratios indicate similar sensitivities (ratios range of 0.8 to 1.2), and 36% indicate humans are more sensitive than mice (ratios > 1.2). However, the exposure conditions of the human patch test relative to those of the MEST should theoretically bias the comparison towards finding humans more (not less) sensitive than mice. The patch test (in which an occlusive patch is left in place for 2- 4 days) represents more severe exposure conditions than those of the MEST. These exposure conditions would be expected to induce human irritation at relatively lower doses than exposure conditions similar to those of the MEST.

The available data do not support the use of a 10-fold uncertainty factor to extrapolate results in mice to humans. However, confidence in the accuracy of the estimates of the mouse and human notes precludes using an uncertainty factor of 1 for interspecies differences. Thus, an uncertainty factor of 3 was selected as the interspecies uncertainty factor. The estimated human $NOEL_{ICD}$ (ICD) for a solution of phenol is 0.12 mg/cm^2 skin (mouse $NOEL_{ICD}$ of 0.36 mg/cm^2 skin/uncertainty factor of 3).

Dose-response assessments based on the systemic non-cancer effects of chemicals also use an uncertainty factor to compensate for variation in the human population (i.e., intraspecies differences). The magnitude of this uncertainty factor is usually 3 or 10 (US EPA, 2002). Experimental data on a variety of substances support the use of an uncertainty factor of 10 for systemic non-cancer effects when chemical-specific data on intraspecies differences are not available (US EPA, 2002). Similarly, an intra-species uncertainty factor of 10 has been recommended for use in risk assessment for the induction of ACD (Felter et al., 2002, 2003). It is also used here.

Thus, an estimate of the skin reference dose based on ICD (Skin RfD_{ICD}) for phenol in solution is 0.012 mg/cm^2 skin (human $NOEL_{ICD}$ of 0.12 mg/cm^2 skin/uncertainty factor of 10).

Equation to Calculate Soil Cleanup Objectives Based on Irritant Contact Dermatitis Data for Phenol

Under the MEST, the entire amount of phenol applied to the surface of the skin in a solution is expected to remain on the skin after the solvent evaporates. This amount is 0.012 mg/cm^2 skin at the Skin RfD_{ICD} for phenol. The concentration of phenol in soil needed to obtain this same skin loading dose (i.e., the SCO for phenol) depends on the soil adherence factor (SAF) and the dermal absorption fraction (AF), and can be calculated with the following equation.

If

$$\text{Skin } RfD_{ICD} = SCO \times CF \times SAF \times AF$$

then:

$$SCO = \text{Skin } RfD_{ICD} / (CF \times SAF \times AF)$$

where:

SCO = soil cleanup objective, expressed as soil concentration (mg contaminant/kg soil, or ppm),

Skin RfD_{ICD} = skin reference dose based on irritant contact dermatitis (mg contaminant/cm^2 skin),

CF = unit conversion factor (1 kg soil/1,000,000 mg soil)

SAF = soil adherence factor (mg soil/cm^2 skin)

AF = dermal absorption fraction (unitless fraction)

The US EPA (2004) recommends a range of potentially relevant estimates for the amount of soil adhering to skin (soil adherence fraction, or SAF). The values selected for use in this equation are the same values as those selected for use in equations to estimate dermal absorption into the body from contaminants in soil (see Section 5.2.2.3, Exposure Assessment Parameters and Values – Dermal Pathway). These values are:

Land Use Category	Population	Soil Adherence Factor (mg/cm^2 skin
unrestricted, residential and residential restricted	children	0.2
	adults	0.07
commercial	children and adults	0.2
industrial	adolescents	0.07
	adults	0.2

The US EPA (2004) recommends estimates of the percentage of contaminant in soil that can penetrate the epidermis and enter the dermis (i.e., dermal absorption fraction). The value selected for use is 0.1, which is the same values selected for use to estimate dermal absorption into the body from SVOC contaminants in soil (see Table 5.2.2.3-1). It is the generic value for SVOCs and the value used in this document to estimate the dermal absorption of phenol into the body (Table 5.2.2.3-2).

The parameter values that are used in the calculation of SCOs for phenol are provided below.

Land Use Category	Population	Skin RfD_{ICD}	Exposure Parameter	
			SAF	AF
unrestricted, residential and residential restricted	children	0.012 mg/cm^2 skin	0.2	0.1
	adult		0.07	0.1
commercial	children and adults		0.2	0.1
industrial	adolescents		0.07	0.1
	adults		0.2	0.1

Nickel

Two mice NOELs (0.068 and 0.27 mg/cm^2 skin) were identified for nickel as nickel sulfate. The lower of the two estimates will be used to derive a nickel SCO_{ICD}. Application of the same uncertainty factors as applied to the phenol mouse $NOEL_{ICD}$ yields 0.0023 mg/cm^2 skin as an estimate of a Skin RfD_{ICD} for nickel (0.068 mg/cm^2 skin/30). Studies on the dermal absorption of nickel in soil were not found, and the US EPA does not have a recommended dermal absorption fraction for nickel in soil (see Table 5.2.2.3-1). However, a dermal absorption fraction of 0.01 was chosen based on published results from limited studies of nickel salts directly applied to human skin (Hostynek et al., 2001; Tanojo et al., 2001).[1] This value is higher than the fraction recommended by the US EPA (2004) for cadmium in soil (0.001), but lower than the fraction recommended for arsenic in soil (0.03). The parameter values that are used in the calculation of SCOs for nickel are provided below.

Land Use Category	Population	Skin RfD_{ICD}	Exposure Parameter	
			SAF	AF
unrestricted, residential and residential restricted	children	0.0023 mg/cm^2 skin	0.2	0.01
	adult		0.07	0.01
commercial	children and adults		0.2	0.01
industrial	adolescents		0.07	0.01
	adults		0.2	0.01

Chromium VI

A mouse $NOEL_{ICD}$ (0.049 mg/cm^2 skin) was identified for chromium VI as potassium dichromate. Application of the same uncertainty factors as applied to the other mouse NOELs

[1] This value was derived from limited studies that estimated the percentage of applied nickel that penetrated various layers of the human epidermis both *in vivo* and *in vitro*. It was considered adequate for use in this exploratory analysis of ICD. The studies did not determine the percentage that entered general circulation within the body. Thus, they did not provide data that could be recommended for use to calculate dermal absorption of nickel into the body (see Section 5.2.2.3, Exposure Assessment Parameters and Values – Dermal Pathway).

yields 0.0016 mg/cm^2 skin as an estimate of a Skin RfD_{ICD} for chromium VI (0.049 mg/cm^2 skin/uncertainty factor of 30). Studies on the dermal absorption of chromium in soil were not found. A dermal absorption fraction of 0.04 was chosen from the estimate derived from studies on the dermal absorption of aqueous solutions of sodium chromate in guinea pigs (Wahlberg and Skog, 1963).[2] This value is higher than the fraction recommended by the US EPA (2004) for cadmium in soil (0.001), and similar to the fraction recommended for arsenic in soil (0.03). The parameter values that are used in the calculation of SCOs for chromium VI are provided below.

Land Use Category	Population	Skin RfD_{ICD}	Exposure Parameter	
			SAF	AF
unrestricted, residential and residential restricted	children	0.0016 mg/cm^2 skin	0.2	0.04
	adult		0.07	0.04
commercial	children and adults		0.2	0.04
industrial	adolescents		0.07	0.04
	adults		0.2	0.04

Surrogate Value for Semi-Volatile Organic Compounds (SVOCs)

A mouse $NOEL_{ICD}$ of 0.04 mg/cm^2 skin was identified as a surrogate $NOEL_{ICD}$ for SVOCs lacking chemical specific-data on irritant potency. Application of the same uncertainty factors as applied to other mouse $NOEL_{ICD}$ yields 0.0013 mg/cm^2 skin as an estimate of a surrogate Skin RfD_{ICD} (0.04 mg/cm^2 skin/uncertainty factor of 30). The absorption fraction of 0.1, which is the US EPA (2004) recommended generic value for SVOCs was chosen as the value for use with the surrogate SVOC. The use of US EPA (2004) recommended dermal absorption fractions for individual SVOCs (i.e., 0.03 – 0.05 for pesticides, 0.13 for benzo(a)pyrene, and 0.25 for

[2] This value was derived from a limited study that estimated the percentage of aqueous chromate solutions that penetrated guinea pig epidermis during a 5-hour exposure. It was considered adequate for use in this exploratory analysis of ICD. The study had a limited exposure period and did not determine quantitatively the percentage of the applied dose that that entered general circulation within the body. Thus, the study did not provide data that could be recommended for use to calculate dermal absorption of chromium into the body (see Section 5.2.2.3, Exposure Assessment Parameters and Values – Dermal Pathway).

pentachlorophenol, Table 6) would alter the resultant SCOs, but the goal of the analysis (a generic SCO applicable to all SVOCs) does not warrant the use of contaminant-specific absorption fractions with surrogate chemical irritancy data. The parameter values that are used in the calculation of SCOs for a surrogate SVOC, applicable to SVOCs and pesticides, are provided below.

Land Use Category	Population	Skin RfD_{ICD}	Exposure Parameter	
			SAF	AF*
unrestricted, residential and residential restricted	children	0.0013 mg/cm^2	0.2	0.1
	adult		0.07	0.1
commercial	children and adults		0.2	0.1
industrial	adolescents		0.07	0.1
	adults		0.2	0.1

Discussion

A major limitation of this method for deriving soil cleanup objectives based on toxicity data for irritant contact dermatitis is the lack of appropriate dose-response data for the identification of no-observed-effect levels (NOELs) for ICD in animals or humans. The focus of regulatory toxicology has been the classification of the irritation potency of the undiluted chemical (e.g., non-irritant, slight irritant, moderate irritant, or severe irritant), and not the estimation of NOELs. Thus, other sources of information on the potency of chemicals to cause ICD were used to estimate NOELs for chemicals. Confidence in the resultant estimates is limited because the data were not collected to estimate NOELs, and plausible assumptions were necessary to generate NOELs. Moreover, much of the data were limited to chemicals that were studied because they were potent irritants and/or because they were known to induce allergic contact dermatitis. Thus, useful data on target contaminants were limited to three contaminants (phenol, nickel, and chromium VI). Moreover, the organic chemicals used as surrogates for SVOC target contaminants might be more potent irritants than are likely to be found at Brownfield sites.

The limited data on the relative sensitivities of humans and mice to the irritant potencies of chemicals supports the use of mouse data in the development of animal NOELs for ICD. Moreover, the methods and dose metric used to estimate mouse NOEL for ICD (i.e., mg contaminant per cm^2 skin), and to extrapolate those results to humans are consistent with recent developments in risk assessments for allergic contact dermatitis.

The toxicity data on ICD used to estimate NOELs were generated from studies of the irritant properties of chemicals in solution. Data on the irritant potency of chemicals in soil were not found. Thus, it was assumed that the irritant potency of a chemical in solution is similar to its irritant potency in soil matrix when the skin-loading dose (mg contaminant/cm^2 skin) are equal (i.e., RfD_{ICD} in solution = RfD_{ICD} in soil matrix). The soil concentration at which the skin-loading dose equals the RfD_{ICD} was identified as the SCO_{ICD}. It is calculated from the RfD_{ICD} using factors to compensate for soil adherence and dermal absorption.

Although a dermal absorption fraction recommended by the US EPA was used in the derivation of the SCO for phenol and the SVOC surrogate, the value was not specific to any chemical but was a default value for all SVOCs. The US EPA recommendation, however, is for use in estimating the systemic absorption from dermal exposures. Their use for estimating doses for irritant contact dermatitis is reasonable but uncertain. The dermal absorption fractions used in the derivation of the SCOs for nickel and chromium VI were based on limited experimental data on nickel and chromium VI compounds. Additional uncertainty is also associated with the soil adherence factors.

Each SCO_{ICD} is based on the assumption that the contaminant is in the soil matrix. This may not be true at contaminant soil concentrations that exceeded the soil saturation level for the contaminant. The soil saturation level of a contaminant (C_{sat}) corresponds to the contaminant concentration in soil at which the absorptive limits of the soil particles, the solubility limits of the soil pore water, and saturation of soil pore air have all been reached (US EPA, 1996). At higher concentrations, the soil contaminant in not likely to be incorporated into the soil matrix. Rather, it is likely to be present in a free phase (e.g., nonaqueous phase liquids for contaminants that are

liquid at ambient soil temperatures, and pure solid phases for compounds that are solid at ambient soil temperatures) (US EPA, 1996).

At these concentrations, the values for soil adherence factors and dermal absorption fractions used to calculate SCOs may not be applicable to a contaminant that is in a separate phase and therefore not bound to soil. Thus, any calculated SCO that appears, mathematically, to be protective of ICD, but that exceeds the C_{sat} for the contaminant, is not an appropriate value for evaluating the likelihood of ICD from the soil contaminant. This is because the exposure conditions at concentrations above C_{sat} are not described accurately by the exposure equation.

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Figure 1. Cumulative Frequency Curve of Estimates of Mouse No-Observed-Effect Levels (NOELs) for Irritant Contact Dermatitis for 89 Chemicals (NOELs from Table 4).

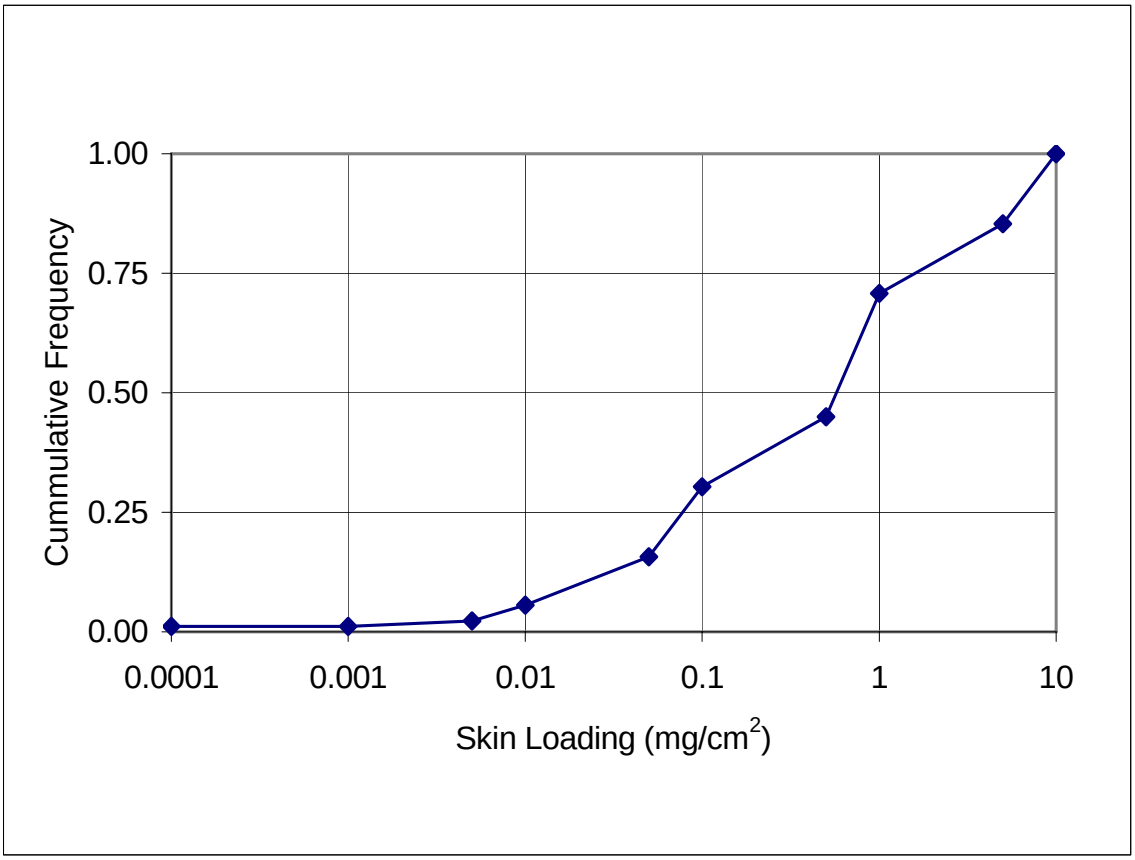

Table 1. Causes of Irritant Contact Dermatitis (English, 2004).

wet work (immersion in water)
degreasing agents
detergents
organic solvents
metal working fluids
surfactants
abrasive materials (dust/friction)
desiccants
acids and bases
enzymes
concentrated salt solutions

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Table 2. Chemicals and Their Challenge Concentrations and Skin Loading Doses for the Mouse Ear Swelling Test (MEST) or the Mouse Ear Swelling Assay (MESA).

Chemical	Challenge			Skin Loading Dose[c] (mg/cm^2 skin)	Ref.
	Concentration[a] (Percentage)	Volume (mcL/ear)	Dose[b] (mg/ear)		
Acetone	100	20	20	7.1	3
Aluminum chloride	10	20	2	0.71	3
p-Aminobenzoic acid	10 (S)	20	2	0.71	3
Benzalkonium chloride	3 (T/I)	20	0.6	0.21	3
Benzene	100	20	20	7.1	3
Benzoic acid	20 (S)	20	4	1.4	3
Benzoyl peroxide	10 (S/I)	20	2	0.71	3
2,4-Hexadiyn-1,6-bis-p-toluene sulfonate	20 (S)	20	4	1.4	3
Butantrone 10-butyryl dithranol	0.14	20	0.03	0.011	17
Butyl acetate	50	20	10	3.6	3
n-Butyl acrylate	>30	25	>7.5	>2.7	5
C_0DGE (a diglycidyl ether)	10 (S)	20	2	0.71	3
C_2DGE (a diglycidyl ether)	20 (T/I)	20	4	1.4	3
Cinnamaldehyde	85	12.5	11	3.9	8
	10	20	2	0.71	3
	10	40	4	1.4	15
Croton oil	0.05	20	0.01	0.0036	3
Cyclohexanone	100	20	20	7.1	3
Dansyl cloride	1	20	0.2	0.071	3
Dicyclohexylcarbodiimide	0.06	100 (25 mcL/d)(4d)[d]	0.06	0.021	6
Dicyclohexylmethane diisocyanate	0.1 (1 mcg/mcL)[e]	40	0.04	0.014	16
	0.1	40	0.04	0.014	13
Diisopropylcarbodiimide	3	100 (25 mcL/d) (4d)[d]	3	1.1	6
Dimethyl amine resin	10	20	2	0.71	3
Dimethyl sulfoxide	100	20	20	7.1	3
Dinitrochlorobenzene	0.3	20	0.06	0.021	9
	1	25	0.25	0.090	4
	1	20	0.2	0.071	3
	0.5	40	0.2	0.071	14

Chemical	Challenge			Skin Loading Dose[c] (mg/cm^2 skin)	Ref.
	Concentration[a] (Percentage)	Volume (mcL/ear)	Dose[b] (mg/ear)		
Dinitrofluorobenzene	0.15	25	0.038	0.014	1
	0.2	12.5	0.025	0.0090	7,8
	0.1, 0.2, 0.5	40	0.04, 0.08, 0.2	0.014, 0.028, 0.071	10
	0.2	25	0.05	0.018	2
	0.1 (T/I)	20	0.02	0.0071	3
	0.5	25	0.12	0.043	6
	0.1	40	0.04	0.014	14
Diphenylmethane-4,4'-diisocyanate	0.5 (5 mcg/mcL)[e]	40	0.2	0.07	16
Disperse blue 3	0.38 (S)	40	0.15	0.054	11
Disperse red 11	0.54 (S)	40	0.22	0.079	11
Dithranol (Anthralin)	0.002	20	0.0004	0.00014	17
Electronics chemical mixture	1 (S)	20	0.2	0.07	3
Ethanol	95	20	19	6.8	3
Ethyl acrylate	30	25	7.5	2.7	5
Ethylenediamine	1	25	0.25	0.090	2
	5	20	1	0.36	3
Eugenol	50 (S)	20	10	3.6	3
Fluorinated graphite	10 (S)	20	2	0.71	3
Formalin (40% CH_2O)	15	25	3.8	1.4	11
	10	40	4	1.4	12
	10	20	2	0.71	3
Fragrance mixture	50 (S)	20	10	3.6	3
Fragrance mix F-07	100	40	40	14	15
Fragrance mix F-16	50	40	20	7.1	15
Fragrance mix F-22	50	40	20	7.1	15
Glutaraldehyde	2.5	25	0.63	0.23	1
	2	25	0.5	0.18	2
	3, 10	40	1.2, 4	0.43, 1.4	12
	10	20	2	0.7	3
Glycerol	100	20	20	7.1	3
Hexachlorophene	10 (T)	20	2	0.71	3

Chemical	Challenge			Skin Loading Dose[c] (mg/cm^2 skin)	Ref.
	Concentration[a] (Percentage)	Volume (mcL/ear)	Dose[b] (mg/ear)		
Hexamethylene diisocyanate	0.5 (T/I)	20	0.1	0.036	3
	0.25 (2.5 mcg/mcL)[e]	40	0.1	0.036	16
Hexamethylenimine	5 (T)	20	1	0.36	3
Hydrochloric acid	5	20	1	0.36	3
Hydroxy citronelol	50 (S)	20	10	3.6	3
Hydroxylamine sulfate	10 (S)	20	2	0.71	3
Isoeugenol	50 not irritating (any dose)	25	12	4.3	4
	10	40	4	1.4	15
Lauric acid	10 (S/I)	20	2	0.71	3
Limonene	50 (S)	20	10	3.6	3
Linseed oil	50 (S)	20	10	3.6	3
m-Phenylenebisoxazoline	20 (S)	20	4	1.4	3
Methylethylketoxime	50 (S)	20	10	3.6	3
Methyl ethyl ketone	100	20	20	7.1	3
Methyl methacrylate	50 (S)	20	10	3.6	3
N,N-Dimethyl-p-nitrosoaniline	0.3 (T/I)	20	0.06	0.021	3
N-[2,4-Epoxypropyl]-phthalimide	10 (S)	20	2	0.71	3
Neomycin sulfate	1 (S)	20	0.2	0.071	3
Nickel sulfate	2	25	0.5	0.18	2
	10 (I/S)	20	2	0.71	3
Oxazolone	0.1	20	0.02	0.0071	3
	1[f]	25	0.25	0.090	2
Phenol	5 (I/T)	20	1	0.36	3
p-Phenylenediamine	1	25	0.25	0.090	4
	10	20	2	0.71	3
Phthalic anhydride	10 (S)	20	2	0.71	3
Picryl chloride	0.5	20	0.1	0.036	3
	0.5	40	0.2	0.071	13
Polyacetylenic diol Short-chained polymer A	1 (S)	20	0.2	0.071	3
Short-chained polymer B	5 (S)	20	1	0.36	3
Short-chained polymer salt A	5 (S)	20	1	0.36	3

Chemical	Challenge			Skin Loading Dose[c] (mg/cm^2 skin)	Ref.
	Concentration[a] (Percentage)	Volume (mcL/ear)	Dose[b] (mg/ear)		
Short-chained polymer salt B	5 (S)	20	1	0.36	3
Potassium dichromate	2	20	0.4	0.14	3
Propyl alcohol	100	20	20	7.1	3
Propylene glycol	100	20	20	7.1	3
Salicylic acid	10 (S)	20	2	0.71	3
Sodium lauryl sulfate	10	20	2	0.71	3
Sodium metasilicate	6 (MIC)[g]	12.5	0.75 (MIC)[g] 0.50 (MNC)[g]	0.27 (MIC) 0.18 (MNC)	7
Solvent red 1	0.49	25	0.12	0.043	11
	0.56	40	0.22	0.079	12
Sudan III	1 (S)	20	0.2	0.071	3
Sulfanilic acid	1 (S)	20	0.2	0.071	3
Surfactant A	10 (T)	20	2	0.71	3
Surfactant B	1 (T/I)	20	0.2	0.071	3
Surfactant C: tetraalkyl ammonium salt of alkyl phosphate acid ester	0.5 (T/I)	20	0.1	0.036	3
3,3,4,5-tetrachlorosaliclanilide (TCSA):	1	20	0.2	0.071	3
Tetramethyl amine resin	5	20	1	0.36	3
Thioglycerol	10	20	2	0.71	3
Toluene diisocyanate	0.5 (T/I)	20	0.1	0.036	3
	0.25 (2.5 mcg/mcL)[e]	40	0.1	0.036	16
Trichloroacetic acid	10	20	2	0.71	3
Trimethylol propane triacrylate	0.3	25	0.075	0.027	5
Tween 80	50(S)	20	10	3.6	3
Vanillin	50 (S)	20	10	3.6	3
Water treatment flocculent	100	20	20	7.1	3

[a]Challenge concentrations are generally assumed to be maximum non-irritating concentrations except as limited by solubility (S), systemic toxicity (T), or a combination of solubility and irritation (S/I or I/S) or of toxicity and irritation (T/I or I/T) (Ref 3).

[b](mg/ear) = (mcL/ear) x (1 mg/mcL) x (Challenge Conc/100)

[c](mg/cm^2) = (mg/ear) / (cm^2/ear). The skin area for both sides of a mouse ear has been estimated to be 2.8 cm^2 (Ref 18).

[d]The challenge consisted of 4 sequential daily doses applied to the mouse ear. The total dose is the dose reported.

[e]The concentration was reported as micrograms per microliter and was converted to percent assuming that the density of the solution was approximately 1 gram per milliliter (or 1000 micrograms per microliter).

[f]*This* concentration was *not* a non-irritating concentration.

[g]MNC = maximum non-irritating concentration = 4%. MIC = minimum irritating concentration = 6%. The *challenge* concentration was a MIC (not an MNC as is generally used).

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Table 3. Uses of Chemicals That Are Known Human Sensitizers and Were Identified as Potent Irritants by the Mouse Ear Swelling Test (MEST).

Chemical	Skin Loading Dose at Mouse NOEL* (mg/cm^2)	Uses	Reference
Dithranol (Anthralin)	0.00014	drug	Medline Plus, 2005; Viluksela et al., 1990**
Croton oil	0.0036	research chemical	Junior et al., 2003
Dinitrofluorobenzene	0.0071 - 0.071	laboratory reagent	HSDB, 2005a
Oxazolone	0.0071 - 0.090	research chemical	Kojima et al., 2004
Butantrone (10-butyryl dithranol)	0.011	potential drug	Viluksela et al., 1990**
Dicyclohexylmethane diisocyanate	0.014	polyurethane and electronic industry; plastic, paints, and pesticides	Stadler and Karol, 1985**; Thorne et al., 1987**
Dicyclohexylcarbodiimide	0.021	research chemical	Hayes et al., 1998**
N,N-Dimethyl-p-nitrosoaniline	0.021	printing fabrics, dyestuff intermediate, chemical intermediate in organic compounds, accelerator for rubber vulcanization	HSDB, 2005b
Dinitrochlorobenzene	0.021 - 0.090	in the manufacture of azo dyes and as a laboratory reagent	HSDB, 2005c
Trimethylol propane triacrylate	0.027	paints, inks, plastics and adhensive	Hayes and Meade, 1999**
Hexamethylene diisocyanate	0.036	plastic, paints, and pesticides	Thorne et al., 1987**
Surfactant C: tetraalkyl ammonium salt of alkyl phosphate acid ester	0.036	surfactants are widely used in cleaning products paints, coatings & inks, emulsion polymerization, personal care products, and agrochemicals	DOW (2005)
Toluene diisocyanate	0.036	plastic, paints, and pesticides	Thorne et al., 1987**
Picryl chloride	0.036 - 0.071	research chemical	Stadler and Karol, 1985** HSDB, 2005d
Solvent red 1	0.043 - 0.079	coloring fats, oil, waxes, smoke, and plastics	HSDB, 2005e

*Skin Loading Dose taken from Table 2.
** Table 2; other references given below.

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Table 4. Data on the Dermal Irritant Potential of Priority List Contaminants: Recommended Concentrations for Human Patch Tests (de Groot, 1994).

Contaminant	Patch Test: Recommended Concentration (solvent)
Volatile Organic Compounds	
Acetone	10% (olive oil)
Benzene	5% (olive oil)
2-Butanone (Methyl ethyl ketone)	not listed
n-Butylbenzene	not listed
sec-Butylbenzene	not listed
*tert-B*utylbenzene	not listed
Carbon tetrachloride	10% (olive oil)
Chlorobenzene	5% (olive oil)
Chloroform	40% (olive oil)
1,2-Dichlorobenzene	1 % (petrolatum) or 5% (alcohol or chloroform)
1,3-Dchlorobenzene	not listed
1,4-Dichlorobenzene	1% (alcohol) or 5% (chloroform)
1,1-Dichloroethane	not listed
1,2-Dichloroethane	50% (olive oil)
1,1-Dichloroethene	not listed
1,2-Dichloroethene (cis)	not listed
1,2-Dichloroethene (trans)	not listed
1,4-Dioxane	0.5% or 1% (water)
Ethylbenzene	10% (petrolatum)
Methyl tert-butyl ether	not listed
Methylene chloride	not listed
n-Propylbenzene	not listed
Tetrachloroethene	1% or 2.5% (olive oil)
Toluene	50% (olive oil)
1,1,1-Trichloroethane	1% (olive oil)
Trichloroethene	5% or 10% (olive oil)
1,2,4-Trimethylbenzene	not listed
1,3,5-Trimethylbenzene	not listed
Vinyl chloride	not listed
Xylenes	50% (olive oil)
Semi-Volatile Organic Compounds	
Acenaphthene	not listed
Acenaphthylene	not listed
Anthracene	pure
Benz[a]anthracene	not listed
Benzo[b]fluoranthene	not listed
Benzo[k]fluoranthene	not listed
Benzo[g,h,i]perylene	not listed
Benzo[a]pyrene	not listed

Chrysene	not listed
Dibenz[a,h]anthracene	not listed
Dibenzofuran	not listed
Fluoranthene	not listed
Fluorene	not listed
Hexachlorobenzene	not listed
Indeno[1,2,3-cd]pyrene	not listed
2-Methylphenol	not listed
3-Methylphenol	not listed
4-Methylphenol	1%-2% (water); 1%, 2%, or 4% (petrolatum)
Naphthalene	2% (alcohol)
Pentachlorophenol	1% (petrolatum, alcohol, or water); 3% (petrolatum)
Phenanthrene	1% (petrolatum)
Phenol	0.5% or 1% (water)
Pyrene	not listed
Pesticides	
Aldrin	1% (petrolatum)
alpha-Chlordane	not listed, but 5% (acetone) for chlordane
4,4'-DDD	not listed
4,4'-DDE	not listed
4,4'-DDT	1% (petrolatum or acetone), 5% (methyl ethyl ketone)
Dieldrin	1% (petrolatum)
Endosulfan I	not listed, 0.5% or 1% (petrolatum) as endosulfan
Endosulfan II	
Endosulfan sulfate	
Endrin	not listed
Endrin aldehyde	not listed
Endrin ketone	not listed
Heptachlor	not listed
alpha-Hexachlorocyclohexane	not listed
beta-Hexachlorocyclohexane	not listed
delta-Hexachlorocyclohexane	not listed
gamma-Hexachlorocyclohexane (lindane)	1% (petrolatum or acetone)
2-(2,4,5-trichlorophenoxy)propionic acid	not listed
Inorganics*	
Arsenic (III)	As(III) (in starch): 3.8% *from:* 5% As_2O_3 (x 150/198)
Barium (II)	Ba (II) (in water): 1.6% *from:* 2% (BaS) (x 137/169)

Beryllium (II)	Be (II) in water: 0.06% *from:* 1% ($BeCl_2$) (x 9/152)
Cadmium (II)	Cd (II) in water: 0.5% *from:* 1% ($CdCl_2 \cdot 2.5H_2O$) (x 112/228)
Chromium (III)	Cr (III) in water: 0.1% *from:* 0.5% $CrCl_3 \cdot 6H_2O$ (x 52/266)
Chromium (VI)	Cr (VI) in petrolatum: 0.2 - 0.7% *from:* 0.5 - 2% ($K_2Cr_2O_7$) (x 104/294)
Copper (II)	Cu (II) in water: 0.3% *from:* 1% ($CuSO_4 \cdot 5H_2O$) (x 64/250) *or* Cu (II) in petrolatum: 4% from 5% CuO (x 64/80)
Cyanide	not listed
Lead (II)	Pb (II) in water: 0.3-0.5% *from:* 0.5-1% [$Pb(C_2H_3O_2)_2 \cdot 3H_2O$] (x 207/379)
Manganese (IV)	Mn (IV) in petrolatum: 4% *from:* 6% (MnO_2) (x 55/87)
Mercury (II)	Hg (II) in petrolatum: 0.05% *from:* 0.07% ($HgCl_2$) (x 201/272)
Nickel (II)	Ni (II) in petrolatum: 0.3% *from:* 1.2% ($NiCl_2 \cdot 6H_2O$) (x 59/238)
Selenium (IV)	Se (II) in petrolatum: 1% *from:* 1.4% (SeS) (x 79/111)
Silver (I)	Ag (I) in water: 0.6 - 1.3% *from:* 1-2% ($AgNO_3$) (x 108/170) *or* 2% (AgBr) (x 108/188) Ag^0 (colloidal silver) in petrolatum: 0.1%
Zinc (II)	Zn (II) in petrolatum: 6% *from:* 8% (ZnO) (x 65.4/81.4)[a] Zn (II) in water: 0.5-0.7% *from:* 1.8% ($ZnSO_4 \cdot H_2O$) (x 65/179)[a] *or* 1.0% ($ZnCl_2$) (x 65/136)

[*] Recommended patch test concentrations for a specific inorganic compound were converted to concentrations for a target atom (X) as follows:

(Concentration, compound) x
[(atomic weight) x (number of atoms of X/molecule)] / (molecular weight).

The molecular weights used included the indicated number of molecules of water of hydration.

Table 5. Comparison of Mouse NOEL and Human NOELs for 18 Chemicals.

Chemical	Mouse Ear Swelling Test[A]		Human Patch Test[B]				
			Recommended Concentration (%)	Finn Chamber		Hill Top Chamber	
	Challenge Concentration (%)	NOEL [mg/cm^2 skin][C]		NOEL [mg/cm^2 skin][D]	Mouse NOEL / Human NOEL	NOEL [mg/cm^2 skin][E]	Mouse NOEL / Human NOEL
Aluminum chloride (hexahydrate)	10	0.71	2	0.6	1.2	3.5	0.20
Benzalkonium chloride	3	0.21	0.1	0.03	7	0.18	1.2
Benzoyl peroxide	10	0.71	1	0.3	2.4	1.8	0.40
Butyl acetate	50	3.6	4	1.2	3	7.1	0.51
Cinnamic aldehyde	10	0.71	1	0.3	2.3	1.8	0.40
Dinitrochlorobenzene	1	0.071	0.03* (0.01 & 0.1)	0.009	7.9	0.053	1.34
2,4-Dinitroflorobenzene	0.1	0.0071	0.01	0.003	2.4	0.018	0.40
Formaldehyde	4	0.29	1	0.3	0.97	1.8	0.16
Glutaraldehyde	10	0.71	1	0.3	2.4	1.8	0.40
Hydrochloric acid	5	0.36	1	0.3	1.2	1.8	0.2
Lauric acid	10	0.71	5	1.5	0.47	8.8	0.080
Phenol	5	0.36	0.71* (0.5 & 1)	0.21	1.6	1.3	0.29
p-Phenylene diamine	10	0.71	1	0.3	2.4	1.9	0.40
Picryl chloride	0.5	0.036	1	0.3	0.12	1.8	0.020
Potassium dichromate	2	0.14	0.5	0.15	0.93	0.88	0.16
Sodium lauryl sulfate	10	0.71	0.1	0.03	24	0.19	4.0
3,3'4'5-Tetrachlorosalicylanilide	1	0.071	0.1	0.03	2.4	0.19	0.40
Thioglycerol	10	0.71	7.1* (5 & 10)	2.1	0.33	13	0.056
Geometric Mean					1.77		0.299

[A]Gad et al. (1986) [B]de Groot (1994); *two recommended concentrations, geometric mean used in analysis.
[C]Dose (mg/cm^2 skin) = % x (0.0714 mg/cm^2-%) (See text).
[D]Dose (mg/cm^2 skin) = % x (0.3 mg/cm^2-%) from Robinson et al. (2000).
[E]Dose (mg/cm^2 skin) = % x (1.77 mg/cm^2-%) from Robinson et al. (2000).

Table 6. Absorption Fractions from EPA Dermal Exposure Guidance (US EPA 2004).

Contaminant	Absorption Fraction*
Arsenic	0.03
Cadmium	0.001
Chlordane	0.04
4,4'-DDT	0.03
gamma-Hexachlorocyclohexane (lindane)	0.04
Benzo(a)pyrene and other PAHs	0.13
Pentachlorophenol	0.25
SVOCs (semi-volatile organic compounds)	0.1

* US EPA (2004) used the term absorption fraction.

Appendix C-2. Hazard Identification on the Potential of Priority Contaminants to be Irritants.

Chemical	CAS RN[1]	Irritant Potential		References
		Human Data	Animal Data	
acenaphthene	83-32-9	Skin, eye, and lung irritant.	No information was found specific to acenaphthene. Coal tar creosote (which contains acenaphthene) is skin irritant in mice and rabbits.	*ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons,* 1995 *NJ Hazardous Substance Fact Sheet: Acenaphthene, 1998*
acenaphthylene	208-96-8	No information was found specific to acenaphthylene. Coal tar creosote (which contains acenaphthylene) is skin, eye, and lung irritant.	No information was found specific to acenaphthylene. Coal tar creosote (which contains acenaphthylene) is skin irritant in mice and rabbits.	*ATSDR Toxicity Profiles for: Poly-cyclic Aromatic Hydrocarbons,* 1995 *Wood Creosote, Coal Tar Creosote, Coal Tar, Coal Tar Pitch, And Coal Tar Pitch Volatiles,* 2002
acetone	67-64-1	Skin, eye, and lung irritant.	Skin irritant in mice. Eye irritant in guinea pigs and rabbits.	*ATSDR Toxicity Profile for Acetone,* 1994 *NJ Hazardous Substance Fact Sheet:* Acetone, 1998
aldrin	309-00-2	Skin and eye irritant.	Potential skin irritant in rabbits.	*ATSDR Toxicity Profile for Aldrin-Dieldrin,* 2002 *NJ Hazardous Substance Fact Sheet:* Aldrin, 2001
anthracene	120-12-7	Skin, eye, and lung irritant; photoirritant to skin.	Photoirritant to mouse skin.	*ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons,* 1995 *NJ Hazardous Substance Fact Sheet: Anthracene, 2002*

arsenic (III) (V)		Skin, eye, and nose irritant.	Skin irritant in mice.	*ATSDR Toxicity Profile for Arsenic,* 2000 *NJ Hazardous Substance Fact Sheets:* multiple sheets on various compounds, 1998-2002
barium (II) - carbonate - nitrate		Skin, eye, and lung irritant.	Barium carbonate is potential skin irritant in rabbits and rats.	*ATSDR Toxicity Profile for Barium,* 1992 *NJ Hazardous Substance Fact Sheet:* Barium nitrate, 2001
benz[a]anthra-cene	56-55-3	No information was found specific to benz[a]anthracene [BaA]. Coal tar pitch (which contains BaA) is skin irritant.	No information was found.	*ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons,* 1995 *NJ Hazardous Substance Fact Sheet: Benz[a]anthracene, 1998*
benzene	71-43-2	Skin, eye, and lung irritant.	Slightly irritating to rabbit skin.	ATSDR Toxicity Profile for Benzene, 1997 NJ Hazardous Substance Fact Sheet: Benzene, 2001
benzo[a]pyrene	50-32-8	Skin and eye irritant.	Chemically reactive with mouse skin; potential skin irritant.	ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons, 1995 NJ Hazardous Substance Fact Sheet: Benzo[b]fluoranthene, 2001
benzo[b]fluor-anthene	205-99-2	Skin and eye irritant.	Chemically reactive with mouse skin; potential skin irritant.	ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons, 1995 NJ Hazardous Substance Fact Sheet: Benzo[k]fluoranthene, 2002

benzo[g,h,i]-perylene	191-24-2	No information specific to benzo[g,h,i]perylene was found. Coat tar pitch, which contains this compound, is skin irritant.	Chemically reactive with skin; potential skin irritant.	ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons, 1995
benzo[k]fluor-anthene	207-08-9	Skin and eye irritant.	Chemically reactive with mouse skin. Prolonged (6 month) exposure results in skin irritation.	.ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons, 1995 NJ Hazardous Substance Fact Sheets: Benzo[a]pyrene, 1998; Coal Tar Pitch, 2001
beryllium		Skin, eye, and lung irritant.	Delayed hypersensitivity and irritation in guinea pig skin.	ATSDR Toxicity Profile for Beryllium, 2002 NJ Hazardous Substance Fact Sheets: Beryllium chloride, 1998 Beryllium carbonate, 2002
n-butylbenzene	104-51-8	Skin and eye irritant.	No information was found.	NJ Hazardous Substance Fact Sheet: Butyl Benzene, 2002
sec-butylbenzene	135-98-8			
tert-butylbenzene	98-06-6			
cadmium		Eye and lung irritant.	Eye irritant in rats (after 2 hour exposure to fumes of cadmium oxide or sulfide).	ATSDR Toxicity Profile for Cadmium, 1999 NJ Hazardous Substance Fact Sheets: Cadmium chloride, 2002; __oxide, 1998; __sulfate, 1998; __sulfide, 1998.
carbon tetrachloride	56-23-5	Skin and eye irritant.	Skin irritant in rabbits and guinea pigs.	ATSDR Toxicity Profile for Carbon Tetrachloride, 1994 NJ Hazardous Substance Fact Sheet: Carbon tetrachloride, 1998
chlordane (technical)	12789-03-6	Skin and eye irritant.	Skin irritant to guinea pigs (after 90 days exposure).	ATSDR Toxicity Profile for Chlordane, 1994 NJ Hazardous Substance Fact Sheet: Chlordane, 1998

chlorobenzene	56-23-5	Skin, eye, and nose irritant.	No information was found.	ATSDR Toxicity Profile for Chlorobenzene, 1990 NJ Hazardous Substance Fact Sheet: Chlorobenzene, 1999
chloroform	67-66-3	Skin, eye, and nose irritant.	Skin irritation in rabbits.	ATSDR Toxicity Profile for Chloroform, 1997 NJ Hazardous Substance Fact Sheet: Chloroform, 1999
chromium (III) - oxide - chloride - sulfate		Chromium oxide, chloride, and sulfate: skin and eye irritants.	Chromium chloride and sulfate: irritants to guinea pig skin.	ATSDR Toxicity Profile for Chromium, 2000 NJ Hazardous Substance Fact Sheets: Chromium (III) oxide,1998; Chromic chloride, 1998; Chromic sulfate, 2002.
chromium (VI) - chromate - dichromate		Skin, eye, and lung irritants.	Skin irritants in rabbits and guinea pigs.	ATSDR Toxicity Profile for Chromium, 2000 NJ Hazardous Substance Fact Sheet: Potassium dichromate, 2002; Potassium chromate, 1996
chrysene (component of coal tar pitch and creosote)	218-01-9	Skin photoirritant.	Potential skin irritant in mice	ATSDR Toxicity Profile for: Poly-cyclic Aromatic Hydrocarbons, 1995 NJ Hazardous Substance Fact Sheet: Chrysene, 1999
copper (II) - chloride - fume/dust - sulfate		Skin, eye, and lung irritants.	Copper sulfate aerosols: throat and lung irritants in mice.	ATSDR Toxicity Profile for Copper, 2002 NJ Hazardous Substance Fact Sheets: Copper chloride, 1999; Copper (dust, fume, or mist), 1999

cyanide (CN) . hydrogen CN . sodium CN		Skin, eye, and lung irritants.	Potential eye irritants in rats.	ATSDR Toxicity Profile for Cyanide, 1997; NJ Hazardous Substance Fact Sheets: Hydrogen cyanide, 1998; Sodium cyanide, 1998
4,4'-DDD	72-54-8	No information was found.	No information was found.	ATSDR Toxicity Profile for DDT, DDE, and DDD, 2002 NJ Hazardous Substance Fact Sheet: DDT, 2002
4,4'-DDE	72-55-9			
4,4'-DDT	50-29-3	Skin, eye, nose, and throat irritant (after prolonged exposure).	Skin irritant in rat, rabbit and guinea pig.	
dibenz[a,h]-anthracene (component of coal tar pitch)	53-70-3	No information was found specific to dibenz[a,h]-anthracene. Coal tar pitch (which contains this PAH) is a skin irritant.	Potential skin irritant in mice.	*ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons,* 1995
dibenzofuran (component of coal tar creosote)	132-64-9	Skin, eye, nose, and throat irritant.	No information was found specific to dibenzofuran. Coal tar creosote (which contains dibenzofuran) is a skin irritant.	*NJ Hazardous Substance Fact Sheet:* Dibenzofuran, 1998
1,2-dichloro-benzene	95-50-1	Skin and eye irritant.	No information was found.	*NJ Hazardous Substance Fact Sheet:* 1,2-dichlorobenzene 1998
1,3-dichloro-benzene	541-73-1	Skin, eye, nose, and throat irritant.	No information was found.	*NJ Hazardous Substance Fact Sheet:* 1,3-dichlorobenzene 1999
1,4-dichloro-benzene	106-46-7	Skin, eye, and nose irritant.	Eye irritant in rat, guinea pig and rabbit.	*ATSDR Toxicity Profile for 1,4-Dichlorobenzene,* 1998 *NJ Hazardous Substance Fact Sheet:* 1,4-Dichlorobenzene, 1998
1,1-dichloro-ethane	75-34-3	Skin, eye, nose, and throat irritant.	No information was found.	*ATSDR Toxicity Profile for 1,1-Dichloroethane,* 1990 *NJ Hazardous Substance Fact Sheet:* 1,1-Dichloroethane, 2001

1,1-dichloro-ethene	75-35-4	Skin, eye, and lung irritant.	Skin and eye irritant in guinea pig.	*ATSDR Toxicity Profile for 1,2-Dichloroethane,* 2001 *NJ Hazardous Substance Fact Sheet:* 1,2-Dichloroethane, 2001
1,2-dichloro-ethane	107-06-2	Skin, eye, nose, and throat irritant.	Nose and throat irritant in rats and mice.	*ATSDR Toxicity Profile for 1,1-Dichloroethene,* 1994 *NJ Hazardous Substance Fact Sheet:* Vinylidene chloride, 1998
cis-1,2-dichloroethene	156-59-2	No irritation data were found		*ATSDR Toxicity Profile for 1,2-Dichloroethene,* 1996 *NJ Hazardous Substance Fact Sheet:* 1,2-Dichloroethylene, 2002
trans-1,2-dichloroethene	156-60-5	Skin, eye, nose, throat, and lung irritant.	Skin irritant in rabbits. Eye irritant in rats.	
dieldrin	60-57-1	Skin and eye irritant.	Potential skin irritant in rabbit.	*ATSDR Toxicity Profile for Aldrin -Dieldrin,* 2002 *NJ Hazardous Substance Fact Sheet:* Dieldrin, 1998
1,4-dioxane	123-91-1	Skin, eye, nose, and throat irritant.	No information was found.	*NJ Hazardous Substance Fact Sheet:* 1,4-Dioxane 2002
endosulfan	115-29-7	Skin and eye irritant.	Skin irritant in rats.	*ATSDR Toxicity Profile for Endosulfan,* 2000 *NJ Hazardous Substance Fact Sheet:* Endosulfan, 1999
endrin	72-20-8	Skin, eye, nose, and throat irritant.	No information was found.	*ATSDR Toxicity Profile for Endrin,* 1996 *NJ Hazardous Substance Fact Sheet:* Endrin, 1998

ethyl benzene	100-41-4	Skin, eye, nose, and throat irritant.	Skin irritant in rabbits.	*ATSDR Toxicity Profile for Ethylbenzene*, 1999 *NJ Hazardous Substance Fact Sheet:* Ethylbenzene, 2002
fluoranthene (component of coal tar pitch)	206-44-0	No information was found specific to fluoranthene. Coal tar pitch, which contains fluoranthene, is a skin irritant.	Potential skin irritant in mice.	*ATSDR Toxicity Profile for Polycyclic Aromatic Hydrocarbons,* 1995
fluorene (component of coal tar creosote)	86-73-7	Skin and eye irritant.	No information was found.	*ATSDR Toxicity Profile for Polycyclic Aromatic Hydrocarbons,* 1995 *NJ Hazardous Substance Fact Sheet: Fluorene 1999*
heptachlor	76-44-8	No information was found.	No information was found.	*ATSDR Toxicity Profile for* Hepta-chlor - Heptachlor Epoxide, 1993 *NJ Hazardous Substance Fact Sheet:* Heptachlor, 2004
hexachloro-benzene	118-74-1	Skin, eye, nose, and throat irritant.	No information was found.	*ATSDR Toxicity Profile for Hexachlorobenzene,* 2002 *NJ Hazardous Substance Fact Sheet:* Hexachlorobenzene, 2001
alpha-hexa-chlorocyclo-hexane	319-84-6	Skin, eye, nose, throat, and lung irritant.	No information was found.	*NJ Hazardous Substance Fact Sheet: alpha-H*exachlorocyclohexane, 2001
beta-hexa-chlorocyclo-hexane	319-85-7	Skin and eye irritant.	No information was found.	*NJ Hazardous Substance Fact Sheet: beta*-Hexachlorocyclohexane, 2001
delta-hexa-chlorocyclo-hexane	319-86-8	No information found.	No information was found..	*ATSDR Toxicity Profile for* Hexachlorocyclohexanes, 1999

gamma-hexa-chlorocyclo-hexane	58-89-9	Skin irritant.	Skin irritant in rats.	*ATSDR Toxicity Profile for* Hexachlorocyclohexanes, 1999 *NJ Hazardous Substance Fact Sheet:* Lindane, 2001
Indeno[1,2,3-cd] pyrene (IP) (a component of coal tar pitch)	193-39-5	No information was found specific to IP. Coal tar pitch, which contains IP, is a skin irritant.	Potential skin irritant in mice.	*ATSDR Toxicity Profile for Polycyclic Aromatic Hydrocarbons,* 1995 *NJ Hazardous Substance Fact Sheet: Indeno[1,2,3-cd)pyrene,* 2000
lead		Eye, nose, and throat irritant.	Aerosols containing inorganic lead compounds are potential lung irritants.	*ATSDR Toxicity Profile for Lead,* 1999 *NJ Hazardous Substance Fact Sheet:* Lead, 2001
manganese (II) - nitrate manganese (IV) - dioxide		Manganese nitrate: skin, eye irritant. Manganese dioxide: nose, throat, and lung irritant.	Organomanganese compounds (e.g., methylcyclopenta-dienyl manganese tricarbonyl) are skin irritants for rabbits.	*NJ Hazardous Substance Fact Sheets:* Manganese dioxide, 1999 Manganese nitrate, 2001 *ATSDR Toxicity Profile for Manganese and Compounds, 2000*
mercury (elemental)	7439-97-6	Skin, eye, and lung irritant.	No information was found.	*NJ Hazardous Substance Fact Sheets: Mercury, 1998*
mercury (I) - oxide - salts		All of these compounds are skin, eye, and lung irritants.	No information was found.	*ATSDR Toxicity Profile for Mercury* (1999) *NJ Hazardous Substance Fact Sheets:* Mercurous oxide, 2001; Mercurous chloride, 2000; __nitrate, 2000; ___sulfate, 2000; and others.

mercury (II) - oxide - salts		All of these compounds are skin, eye, and lung irritants.	No information was found.	*ATSDR Toxicity Profile for Mercury* (1999) *NJ Hazardous Substance Fact Sheets:* Mercuric oxide, 1998; __chloride, 2000; __nitrate. 2000; __sulfate, 2000; and others.
methylene chloride	1634-04-4	Skin, eye, nose, throat, and lung irritant.	Eye irritant in rabbits.	*ATSDR Toxicity Profile for Methylene chloride*, 2000 *NJ Hazardous Substance Fact Sheet:* Methylene chloride, 2001
methyl ethyl ketone (2-butanone)	78-93-3	Skin, eye, nose, and throat irritant.	Skin, eye, throat irritant in rabbits, guinea pigs and rats.	ATSDR Toxicity Profile for 2-Butanone, 1992 NJ Hazardous Substance Fact Sheet: Methyl ethyl ketone, 2002
methyl tert-butyl ether	1634-04-4	Skin, eye, nose, and throat irritant.	Doses to rabbit, guinea pig skin: erythema, irritation.	ATSDR Toxicity Profile for Methyl-tert-butyl ether, 1996 NJ Hazardous Substance Fact Sheet: Methyl-tert-butyl ether, 1998
2-methylphenol	95-48-7	Skin, eye, nose, and throat irritants.	Skin irritants in several species.	ATSDR Toxicity Profile for Cresols, 1992 NJ Hazardous Substance Fact Sheet: Cresols, 1998
3-methylphenol	108-39-4			
4-methylphenol	106-44-5			
naphthalene (component of coal tar creosote)	91-20-3	Skin, eye, nose, and throat irritant.	Skin and eye irritant in rat and rabbit.	ATSDR Toxicity Profile for Naphthalene, 1995 NJ Hazardous Substance Fact Sheet: Naphthalene, 2004

nickel (II) - carbonate - chloride - oxide - sulfate		All of these compounds are skin, eye, nose, and throat irritants.	Skin irritant in rats.	ATSDR Toxicity Profile for Nickel, 1997 NJ Hazardous Substance Fact Sheets: Nickel carbonate, 1999; __chloride, 2002; __oxide, 1999 __ sulfate, 2003
pentachloro-phenol	87-86-5	Skin, eye, nose, and throat irritant.	Skin irritant in rabbit.	ATSDR Toxicity Profile for Penta-chlorophenol, 2001 NJ Hazardous Substance Fact Sheet: Pentachlorophenol, 2002
phenanthrene (component of coal tar creosote)	85-01-8	Skin, eye, nose, and throat irritant.	Potential skin irritant in mice. Coal tar creosote (which contains phenanthrene) is skin irritant.	*ATSDR Toxicity Profile for Polycyclic Aromatic Hydrocarbons,* 1995 *NJ Hazardous Substance Fact Sheet:* Phenanthrene, 1999
phenol	108-95-2	Skin, eye, nose, and throat irritant.	Skin irritant in mice.	*ATSDR Toxicity Profile for Phenol,* 1998 *NJ Hazardous Substance Fact Sheet:* Phenol, 2001
n-propyl-benzene	103-65-1	Skin, eye, nose, and throat irritant.	No information found.	*NJ Hazardous Substance Fact Sheet:* Propyl benzene, 2001
pyrene (component of coal tar pitch)	129-00-0	No irritation data were found.	Potential skin irritant in mice. Coal tar pitch (which contains pyrene) is skin irritant.	*.ATSDR Toxicity Profile for Poly-cyclic Aromatic Hydrocarbons,* 1995
selenium (IV) - dioxide - sulfide		Selenium dioxide is skin, eye, nose, throat, and lung irritant	Selenium sulfide in skin irritant in mice.	*ATSDR Toxicity Profile for Selenium, 2001* *NJ Hazardous Substance Fact Sheet:* Selenium oxide, 2000

silver - elemental		Skin, eye, nose, and throat irritant.	Aerosol containing colloidal silver is nose and throat irritant in rabbits.	*ATSDR Toxicity Profile for Silver, 1990* *NJ Hazardous Substance Fact Sheet: Silver, 2002;* __nitrate, 2000
silver (I) - nitrate		Skin, eye, nose, throat, and lung irritant	No information was found.	
tetrachloro-ethene	127-18-4	Skin, eye, nose, and throat irritant	Nose and throat irritant in dogs.	*ATSDR Toxicity Profile for Tetrachloroethylene, 1997* *NJ Hazardous Substance Fact Sheet:* Tetrachloroethylene, 2002
toluene	108-88-3	Skin, eye, nose, and throat irritant	Skin irritant in guinea pigs.	*ATSDR Toxicity Profile for Toluene,* 2000 *NJ Hazardous Substance Fact Sheet:* Toluene, 1998
1,1,1-trichloro-ethane	71-55-6	Skin, eye, and throat irritant.	Skin irritant in rabbits and guinea pigs.	*ATSDR Toxicity Profile for 1,1,1-Trichloroethane*, 1995 *NJ Hazardous Substance Fact Sheet:* Methyl chloroform, 2001
trichloroethene	79-01-6	Skin and eye irritant.	Skin irritant in guinea pigs.	*ATSDR Toxicity Profile for Trichloroethylene,* 1997 *NJ Hazardous Substance Fact Sheet: T*richloroethylene, 2000
2-(2,4,5-trichlo-rophenoxy)-propionic acid	93-72-1	Skin, eye, nose, throat, and lung irritant.	No information was found.	*NJ Hazardous Substance Fact Sheet: Trichlorophenoxy-propionic acid, 2001*
1,2,4-trimethyl-benzene	95-63-6	Skin and eye irritant.	No information was found.	*NJ Hazardous Substance Fact Sheet:* Trimethyl benzene (mixed isomers), 2003
1,3,5-trimethyl-benzene	108-67-8			

vinyl chloride	75-01-4	Skin, eye, nose, throat, and lung irritant.	Lung irritant in mice, rats and guinea pigs.	*ATSDR Toxicity Profile for Vinyl chloride,* 1997 *NJ Hazardous Substance Fact Sheet:* Vinyl chloride, 2001
xylenes	1330-20-7	Skin, eye, nose, and throat irritant.	Skin irritant in rabbits, guinea pigs and mice	*ATSDR Toxicity Profile for Xylenes,* 1995 *NJ Hazardous Substance Fact Sheet:* Xylenes, 1998
zinc (II) - carbonate - chloride		Skin, eye, nose, and throat irritant.	Zinc chloride is skin irritant in mice, rabbits and guinea pigs.	*ATSDR Toxicity Profile for Zinc,* 1994 *NJ Hazardous Substance Fact Sheet:* Zinc carbonate, 2002

[1]CAS RN: Chemical Abstracts Service Registry Number

References:

ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological Profiles Series. Atlanta GA: U.S. Department of Health and Human Services. (http//www.atsdr.cdc.gov)

In addition to the Toxicity Profiles listed in this document, the following profile addresses the properties of mixtures of polycyclic aromatic hydrocarbons, including coal tar creosote and coal tar pitch:

Wood Creosote, Coal Tar Creosote, Coal Tar, Coal Tar Pitch, And Coal Tar Pitch Volatiles, (2002).

NJ (New Jersey Department of Health and Senior Services). Hazardous Substance Fact Sheet Series. Trenton, NJ: Division of Epidemiology, Environmental and Occupational Health. (http://www.state.nj.us/health/eoh/rtkweb/rtkhsfs.htm)

In addition to the Fact Sheets listed in this document, the following Fact Sheets address the properties of mixtures of polycyclic aromatic hydrocarbons, including coal tar creosote and coal tar pitch:

Coal Tar Creosote (2001); Coal Tar Pitch (2001).