

## APPENDIX A

### ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical name: Hexachlorobenzene  
CAS number: 118-74-1  
Date: May 2002  
Profile status: Draft 3 Post-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 23  
Species: Rat

MRL: 0.008  mg/kg/day  ppm  mg/m<sup>3</sup>  
(LOAEL = 2.5 mg/kg/day; total uncertainty factors = 300)

Reference: Goldey ES and Taylor DH. 1992. Developmental neurotoxicity following prenatally maternal exposure to hexachlorobenzene in rats. *Neurotoxicol and Teratol*, 14: 15–21.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of 30 virgin female Sprague-Dawley rats were dosed by gastric intubation for 4 days with 0, 2.5, or 25 mg/kg/day hexachlorobenzene to achieve a total dose of 0, 10, or 100 mg/kg for the 4-day period. Dosing was completed 2 weeks before breeding. The developmental neurotoxicity of hexachlorobenzene was assessed using a battery of behavioral tests. Negative geotaxis response was assessed in two male and two female pups from each litter on postnatal day (PND) 6, 8, and 10. Olfactory discrimination/homing was assessed in two male and two female pups from each litter on PND 9, 10, and 11. This test simultaneously measures sensory discrimination, motivation, and locomotor ability. The development of exploration and locomotion was assessed in whole litters between PND 15 and 20. Acoustic startle response (ASR) was assessed on PND 23 and 90. Visual discrimination learning, as measured in the water-filled T-maze, was assessed in offspring on PND 40. Motor activity in mature offspring (PND 60) was measured in an open area. These adult animals were again tested for exploratory activity on PND 100.

Effects noted in study and corresponding doses: Hexachlorobenzene affected multiple pathways throughout the developing nervous system, manifested as slight hyperactivity, at a LOAEL of 2.5 mg/kg/day. The offspring rats showed faster response times in negative geotaxis and olfactory discrimination/homing tests at the 2.5 or 25 mg/kg/day maternal dose level. Offspring exposed to maternal doses of 2.5 or 25 mg/kg/day showed either significantly increased exploratory behavior, slight hyperactivity, or both during the early life (19–20 days of age). Hexachlorobenzene-exposed offspring at the 25 mg/kg/day dose level exhibited significantly decreased ASR (23-day-old pups). When rats were tested later as adults (90 days old), response amplitude was significantly elevated in males in both groups exposed *in utero* to 2.5 and 25 mg/kg/day, compared to controls. Maternal exposure of rats to hexachlorobenzene did not result in any significant changes in learning ability, locomotor activity (60-day-old offspring), or exploratory activity (100-day-old offspring).

Dose end point used for MRL derivation:

NOAEL  LOAEL

2.5 mg/kg/day; hyperactivity in offspring.

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Uncertainty factors used in MRL derivation:

1  3  10 (for use of a minimal LOAEL)

1  3  10 (for extrapolation from rats to humans)

1  3  10 (for human variability)

Total uncertainty factors:  $3 \times 10 \times 10 = 300$

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Not applicable.

Was a conversion used from intermittent to continuous exposure?

No.

Other additional studies or pertinent information that lend support to this MRL: Review of the located human and animal oral acute toxicity data for hexachlorobenzene indicate that the 4-day developmental study by Goldey and Taylor (1992) provides the most appropriate data for use deriving oral acute MRL for hexachlorobenzene. The LOAEL of 2.5 mg/kg/day is the most refined LOAEL for the acute toxicity of hexachlorobenzene.

Adverse neurological signs and symptoms have also been observed in human offspring of maternally exposed to hexachlorobenzene. Children of mothers who had eaten hexachlorobenzene-contaminated bread (estimated hexachlorobenzene intake of 0.05–0.2 g/day) in Turkey exhibited muscle weakness, pinched facies, cogwheel rigidity, and sensory shading. Hexachlorobenzene was detected in the breast milk of the mothers, indicating lactational transfer (Cam and Nigogosyan 1963; Peters et al. 1982, 1987). Since hexachlorobenzene crosses the placenta and accumulates in fetal tissues in several animal species including the rat (Cripps 1990; Villeneuve and Hierlihy 1975), rabbit (Villeneuve et al. 1974a), and mouse (Courtney and Andrews 1985; Courtney et al. 1979), it is likely that the human offspring were also exposed to hexachlorobenzene during gestation. Development of neurotoxic signs has also been reported in other neonatal animals. These signs included convulsions, tremors, and progressive weakness in rats (Cripps 1990). Oral hexachlorobenzene has also been shown to interfere with the function of the nervous system in adult animals, inducing tremors, ataxia, and paralysis in unspecified strain of rats (Ockner and Schmid 1961); clonic convulsions, tremors, hyper-excitability, reversible muscle fasciculations, and lethargy in adult Wistar rats (Kennedy and Wigfield 1990; Koss et al. 1978; Nikolaev et al. 1986); mild reduction in conduction velocity of sciatic nerve, denervation, fibrillations, and chronic repetitive discharges in adult Sprague-Dawley rats (Sufit et al. 1986); tremor and hyperexcitability in adult Sherman rats (Kimbrough and Linder 1974); dysrhythmic electroencephalogram in adult Beagle dogs (Sundlof et al. 1981); tremor in adult C57B1/6J mice (Hahn et al. 1988); severe tremors and muscular weakness in adult Rhesus monkeys (Knauf and Hobson 1979); and tremors, panting, and unsteady gait in adult SPF pigs (Den Tonkelaar et al. 1978).

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical name: Hexachlorobenzene  
CAS number: 118-74-1  
Date: May 2002  
Profile status: Draft 3 Post-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 129  
Species: Monkey

MRL: 0.0001  mg/kg/day  ppm  mg/m<sup>3</sup>  
(LOAEL = 0.01 mg/kg/day; total uncertainty factors = 90)

References: Bourque AC, Singh A, Lakhanpal N, et al. 1995. Ultrastructural changes in ovarian follicles of monkeys administered hexachlorobenzene. *Am J Vet Res* 56: 1673–1677.

Jarrell JF, MacMahon A, Villeneuve D, et al. 1993. Hexachlorobenzene toxicity in the monkey primordial germ cell without induced porphyria. *Reproductive Toxicology* 7:41–47.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): In the Jarrell et al. (1993) study, groups of four female *Cynomolgus* monkeys were administered 0, 0.1, 1, or 10 mg/kg/day hexachlorobenzene in gelatin capsules for 90 days. No systemic toxicity was noted in any of the animals. After treatment, the animals were sacrificed and one ovary was removed from each animal from each dose group (including controls) and examined by transmission electron microscopy for alterations to surface epithelium. A cycle of *in vitro* fertilization with oocytes removed from exposed females during the menstrual cycle was performed to evaluate fertility. Induction of ovarian hyperstimulation (performed with human menopausal gonadotropin) was conducted to evaluate oocyte function. In the follow-up Bourque et al. (1995) study, groups of four female *Cynomolgus* monkeys were administered 0, 0.01, 0.1, 1, or 10 mg/kg/day hexachlorobenzene in gelatin capsules for 90 days. Monkeys were then given a preparation containing follicle-stimulating and luteinizing hormones on days 2–7 of the next menstrual cycle to stimulate follicle development, and human chorionic gonadotropin was administered on day 8 of the cycle. Oophorectomy was performed on day 10 of the cycle via laparotomy. The ovary was examined by transmission electron microscopy.

Effects noted in study and corresponding doses: In the Jarrell et al. (1993) study, *in vitro* fertilization and ovarian hyperstimulation in terms of percent fertilization, estradiol response to gonadotropin, follicular development, oocyte recovery rates and maturation, and early embryo development were not significantly different from control animals. Hexachlorobenzene treatment caused a decrease in the total number of oocytes and primordial follicles. Ultrastructural changes in ovarian epithelium included a decrease in nuclear membrane distinction, an increase in density and granularity of oocyte nuclei, an increase in vacuoles, aggregated lysosomes in ooplasm of follicular cells, and pyknotic granulosa cells. The ooplasm of some follicles was necrotic, and some follicles had mild to moderate degenerative changes. These changes were observed in all exposed animals; the severity of symptoms increased in a dose-dependent manner. The follow-up study by Bourque et al. (1995) extended the observation of ultrastructural effects in the ovary to 0.01 mg/kg/day. At this dose, mitochondria in developing follicles were condensed and deformed. At higher doses, the mitochondria were progressively more damaged and additional changes, such as indentation of nuclear membranes and abnormal accumulation of lipid in the cytoplasm of follicular cells, were noted.

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Dose end point used for MRL derivation:

NOAEL  LOAEL

0.01 mg/kg/day; degenerative lesions in ovarian follicles

Uncertainty factors used in MRL derivation:

1  3  10 (for use of a minimal LOAEL)

1  3  10 (for extrapolation from monkeys to humans)

1  3  10 (for human variability)

Total uncertainty factors:  $3 \times 3 \times 10 = 90$

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Not applicable.

Was a conversion used from intermittent to continuous exposure?

No.

Other additional studies or pertinent information that lend support to this MRL: Review of the located human and animal oral intermediate toxicity data for hexachlorobenzene indicate that the 90-day studies by Bourque et al. (1995) and Jarrell et al. (1993) provide the most appropriate data for use in deriving an oral intermediate MRL for hexachlorobenzene.

In humans, 15 fetal deaths (comprising 13 miscarriages and 2 stillbirths) and 173 live births occurred in 42 females in a 4-year period (1977–1981) several years after the widespread accidental ingestion of hexachlorobenzene-treated seed grain in Turkey (Peters et al. 1982, 1987). These mothers also had 0.51 ppm hexachlorobenzene in their breast milk as compared to 0.07 ppm in unexposed controls (Gocmen et al. 1989). It has also been demonstrated that hexachlorobenzene in human milk can readily cross to the child during lactation and accumulate in the offspring (Ando et al. 1985; Weisenberg 1986; Weisenberg et al. 1985).

Animal studies provide additional evidence that hexachlorobenzene is toxic to the mammalian ovary and may interfere with mechanisms regulating ovarian steroidogenesis. Female Cynomolgus monkeys exhibited a dose-dependent decrease in serum progesterone levels during the luteal phase of the menstrual cycle when administered hexachlorobenzene doses of 0.1 (0.1, 1, 10) mg/kg/day as capsules for 90 days; the decrease in levels of progesterone was not observed during the follicular and periovulatory phases. Lengthening of the menstrual cycle was also observed, as well as dose-dependent ultrastructural changes in surface epithelium of the ovary (indicative of cellular degeneration) and changes in ovary surface epithelial cell shape (length to width ratio), in all treatment groups, the severity of which was increased in a dose-dependent manner (Foster et al. 1992a; Sims et al. 1991). Increased serum progesterone levels and elevated ovarian weights were observed in superovulated female Sprague-Dawley rats orally administered 1 mg/kg/day hexachlorobenzene by gavage (in corn oil) for 21 days (Foster et al. 1992b). Serum levels of estradiol and progesterone of female Sprague-Dawley rats receiving daily doses of 50 mg/kg/day hexachlorobenzene by gavage in corn oil for 5 days were not significantly affected, although super-ovulated rats (dosed with pregnant mare serum gonadotropin and human chorionic gonadotropin) exposed to hexachlorobenzene in this study exhibited significant elevation of serum levels of progesterone (Foster et al. 1993). In a subsequent study with ovariectomized female Sprague-Dawley rats administered daily oral

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doses of 1, 10, or 100 mg/kg/day hexachlorobenzene in corn oil by gavage for 30 days, circulating levels of corticosterone levels were reduced by 25 and 51% at the 1 and 10 mg/kg/day hexachlorobenzene dose levels, respectively. Circulating cortisol levels were also significantly reduced ( $p < 0.05$ ). Hexachlorobenzene treatment had no effect on the levels of circulating aldosterone and progesterone levels, or on absolute and relative weights of the adrenal glands. The investigators concluded that hexachlorobenzene exposure induces alterations in steroidogenesis of cells of the adrenal cortex inner zone (Foster et al. 1995b).

A study conducted with female Rhesus monkeys given gavage doses of 8, 32, 64, or 128 mg/kg/day hexachlorobenzene in methylcellulose for 60 days found degenerative changes of the ovarian follicle, stroma, and germinal epithelium at dose levels of 64 mg/kg/day (Iatropoulos et al. 1976). In another monkey study, adult female Rhesus monkeys given oral doses of 8, 16, 32, 64, or 128 mg/kg/day hexachlorobenzene for 60 days showed significantly depressed (29%,  $p < 0.01$ ) whole serum cholesterol levels in weeks 3, 5, and 8. On day 60, depressed serum potassium and elevated SGOT were seen at the 128 mg/kg/day dose level. The authors suggested that the changes in potassium and cholesterol levels may be due to liver histopathology. The authors suggested that the changes in potassium levels may be due to unusual steroidogenic activity associated with changes in ovarian morphology (Knauf and Hobson 1979).

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical name: Hexachlorobenzene  
CAS number: 118-74-1  
Date: May 2002  
Profile status: Draft 3 Post-Public Comment  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to figure: 162  
Species: Rat

MRL: 0.00005  mg/kg/day  ppm  mg/m<sup>3</sup>  
(LOAEL = 0.016 mg/kg/day; total uncertainty factors = 300)

Reference: Arnold DL, Moodie CA, Charbonneau SM, Grice HC, et al. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A. *Food Chem Toxicol*, 23(9): 779–793.

Experimental design (human study details or strain, number of animals per exposure/control group, sex, dose administration details): Groups of Sprague-Dawley rats (40 per sex) of the F<sub>1</sub> generation were exposed to dietary hexachlorobenzene at 0, 0.32, 1.6, 8, or 40 ppm (approximate doses of 0, 0.016, 0.08, 0.4, or 2 mg/kg/day) from weaning for life (130 weeks). The groups of rats were also exposed *in utero* to hexachlorobenzene since variable numbers (40–66 per sex) of the F<sub>0</sub> generation rats, from which the F<sub>1</sub> generation rats used in this study were randomly selected, were exposed to corresponding doses 3 months prior to mating and weaning of the F<sub>1</sub> rats. The F<sub>0</sub> rats were killed and examined at weaning of the F<sub>1</sub> rats. The F<sub>1</sub> rats in this study were sacrificed after the animals had been on test for 130 weeks. A total of 35 tissues and organs (including brain, heart, liver, extrahepatic bile duct, lungs, spleen, pancreas, small intestine, adrenals, kidneys, bladder, ovaries, uterus, skin, pituitary, thyroid, parathyroid, thymus, prostate, testes, and bone) were histopathologically examined.

Effects noted in study and corresponding doses: Significant dose-response trends were observed in both sexes for hepatic basophilic chromogenesis at 0.4 mg/kg/day, and in males for peribiliary lymphocytosis and fibrosis at or greater than the lowest dose tested (0.016 mg/kg/day). Chronic nephrosis, severe in males, and reduced pup viability were observed at 2 mg/kg/day. Tumors were also increased at 2 mg/kg/day, including neoplastic liver nodules in females, parathyroid adenoma in males, and adrenal pheochromocytoma in both males and females. No treatment related effects in the rat offspring were observed with respect to feed consumption or body weight.

For derivation of the MRL, the increased incidences of peribiliary lymphocytosis and fibrosis in treated males were considered to represent a minimal effect. These are common spontaneous lesions in aging rats and occurred in approximately 30% of controls in this study. For peribiliary fibrosis, incidence was increased in all treated groups (statistically significant in the 0.016 and 2 mg/kg/day groups), but there was no clear evidence of a dose-response (13/48, 23/48, 21/48, 21/49, and 23/49 in the control, 0.016, 0.08, 0.4, and 2 mg/kg/day groups, respectively). For peribiliary lymphocytosis, the incidence was increased in all treated groups (statistically significant in the 0.016, 0.08, and 2 mg/kg/day groups), and while the trend with dose was not very impressive, it was statistically significant (16/48, 27/48, 26/48, 21/49, and 32/49, respectively). Incidences of these lesions in the control and treated females were similar to the control males (ranging from 6/49 to 14/49), suggesting that the incidence levels in control males were not unusually low. Overall, these findings suggest that hexachlorobenzene produced a



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minimal hepatic effect in male rats at the lowest doses administered by increasing the incidence of age-related hepatic lesions.

Dose end point used for MRL derivation:

NOAEL  LOAEL

0.016 mg/kg/day; peribiliary lymphocytosis and fibrosis of the liver.

Uncertainty factors used in MRL derivation:

1  3  10 (for use of a minimal LOAEL)

1  3  10 (for extrapolation from rats to humans)

1  3  10 (for human variability)

Total uncertainty factors:  $3 \times 10 \times 10 = 300$

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

Yes. Dose = 0.32 ppm or 0.32 mg hexachlorobenzene/kg feed. The average rat consumes 0.05 kg of feed per kg body weight per day (EPA 1986 reference food factor for rats). Thus, the average daily dose of hexachlorobenzene is estimated to be  $0.32 \text{ mg/kg} \times 0.05 \text{ kg feed/kg body weight/day} = 0.016 \text{ mg/kg/day}$ .

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

Not applicable.

Was a conversion used from intermittent to continuous exposure?

No.

Other additional studies or pertinent information that lend support to this MRL: The liver appears to be a target organ of hexachlorobenzene; therefore, using hepatic effects (peribiliary lymphocytosis and fibrosis) to calculate the MRL is appropriate. Also, review of the located human and animal oral chronic toxicity data for hexachlorobenzene indicate that the 130-week rat study by Arnold et al. (1985) provide the most appropriate data to derive a chronic MRL because the study provides the most refined LOAEL for the characteristic chronic toxicity (hepatic effects) of hexachlorobenzene.

Other studies in several animal species have demonstrated that the liver is the major target organ of hexachlorobenzene exposure. Typical signs included microscopic lesions, increased porphyrin levels, and interference with hepatic enzymes involved in the heme biosynthesis pathway.

Oral exposure to hexachlorobenzene induced liver histopathology and altered liver histochemistry in the rats. The relative liver weights of male rats were increased by 46% while those of females were increased by 23% in a study in which both sexes of Sprague-Dawley rats were given oral hexachlorobenzene doses of 27.5 mg/kg/day for 4 weeks (Richter et al. 1981). Cytoplasmic vacuolation, anisokaryosis, and pyknotic hepatocytes were seen in the liver of female Sprague-Dawley rats administered single gavage doses of 400 or 600 mg/kg hexachlorobenzene in corn oil and observed for 14 days. Relative liver weights were increased by 16–18 and 13–18% in the 400 and 600 mg/kg dose group animals, respectively. Serum cholesterol levels were increased by 13–30 and 7–31% in the 400 and 600 mg/kg dose group animals, respectively. No changes in serum sodium, potassium, inorganic phosphorus, total bilirubin, alkaline phosphatase, aspartate aminotransferase, total protein, calcium, glucose, and lactate dehydrogenase content were found. Liver microsomal aminopyrine demethylase, aniline hydroxylase, and ethoxyresorufin deethylase (EROD) activities were unchanged by hexachlorobenzene exposure (Lecavalier et al. 1994). Liver weight was significantly increased by nearly 45% in animals treated with

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1,000 mg/kg/day for 7 days. Liver porphyrin carboxylase activity was significantly decreased in animals receiving 1,000 mg/kg/day (Kleiman de Pisarev et al. 1990). In rats given 100 mg/kg/day of hexachlorobenzene for 60 days, the liver became enlarged, and liver degeneration and increased hepatic porphyrins were observed (Ockner and Schmid 1961). A 67% hepatomegaly was observed in male Wistar (WAG/MBL) rats given oral doses of 120 mg/kg/day hexachlorobenzene, 3 times a week for 4 weeks (van Raaij et al. 1993b). Similarly, an 81% liver enlargement was reported at a hexachlorobenzene dose of 10 mg/kg/day for a group of Fischer 344 rats in a 15-week study. Liver-to-body weight ratios also increased at dose levels of 10 and 25 mg/kg/day (Andrews et al. 1989). Similarly, significantly increased liver weights were observed in rats fed 100 mg/kg/day hexachlorobenzene in the diet for 5 days (Rajamanickam and Padmanaban 1974).

Porphyria, as an index of hepatopathology, was also seen in several animal studies following oral exposure to hexachlorobenzene. Uroporphyrin and hepatic porphyrin accumulation were reported in a 13-week study in female Wistar rats administered 7.5 or 15 mg/kg/day hexachlorobenzene in the feed. Rats in the 7.5 and 15 mg/kg/day dose group exhibited elevated d-ALA synthase levels (94 and 483%, respectively). At the low dose (7.5 mg/kg/day), relative liver weight increased by 31%, and at the highest dose tested (15 mg/kg/day), relative liver weight increased by 103%. Hypertrophic hepatocytes with eosinophilic cytoplasm with thready basophilic structures, as well as inflammatory cell infiltrates, were observed in the livers of animals dosed with 15 mg/kg/day hexachlorobenzene. By the end of the study, uroporphyrin in the 15 mg/kg/day dose group was 1,400% that of control animals. Liver accumulations of porphyrins were 1,054 and 15,104%, respectively, for the 7.5 and 15 mg/kg/day dose group animals compared to undosed controls. Liver retinoid and plasma retinol were decreased by 70 and 53%, respectively, at the 15 mg/kg/day dose level (den Besten et al. 1993).

Female Sprague-Dawley rats exhibited elevated urinary and hepatic porphyrins following administration of 50 mg/kg/day hexachlorobenzene for 12 consecutive days (cumulative dose of 600 mg/kg), and 10 days (2 weeks, 5 days/week, cumulative dose of 500 mg/kg), or 100 mg/kg/day for 5 consecutive days (cumulative dose of 500 mg/kg). The porphyria seen was reported to be similar in severity to that observed in female rats receiving a cumulative dose of 1,500 mg/kg over a 6-week period. Porphyria induced by a cumulative dose of 500 mg/kg (either protocol) persisted for more than 500–600 days after exposure (Krishnan et al. 1991). Similarly, female Wistar rats given hexachlorobenzene in the diet at a dose of 150 mg/kg/day for 107 days exhibited a 91% decrease in uroporphyrinogen decarboxylase activity and 2,888-fold increase in hepatic porphyrin concentration (Elder and Urquhart 1986).

Oral exposure to hexachlorobenzene resulted in altered liver function and histology in: adult female Rhesus monkeys given oral doses of 8, 16, 32, 64, or 128 mg/kg/day hexachlorobenzene for 60 days (Knauf and Hobson 1979); female Wistar rats exposed to 50 mg/kg/day hexachlorobenzene by gavage for 15 weeks (Koss et al. 1978, 1983); female Agus Wistar rats fed diets containing 5 mg/kg/day hexachlorobenzene (with 2% arachis oil) for 75–90 weeks (Smith and Cabral 1980); female Wistar rats exposed to 5 or 50 mg/kg hexachlorobenzene for 56 days (Kennedy and Wigfield 1990); both sexes of Charles River rats fed hexachlorobenzene doses of 0.5, 2, 8, or 32 mg/kg/day (Kuiper-Goodman et al. 1977); monkeys given doses of 8 mg/kg/day for 60 days (Iatropoulos et al. 1976); and adult female Beagle dogs administered 25 mg/kg/day hexachlorobenzene in gelatin capsules for 21 days (Sundlof et al. 1981). Induction of liver microsomal enzymes, increased liver weight, and microscopic lesions were demonstrated at a hexachlorobenzene dose of 5 mg/kg/day, while centrilobular hypertrophy, elevated urinary coproporphyrinogen, and depressed glucose-6-phosphatase activity were observed at a lower dose level (0.5 mg/kg/day) in pigs treated for 90 days (Den Tonkelaar et al. 1978).

Several animal studies also found increased induction of P-450 isozymes and other hepatic enzymes, usually accompanied by hepatic or uroporphyrin, as an index of adverse effects in the liver (Adjarov et al. 1982; Hahn et al. 1988, 1989; Kitchin and Brown 1989; Kleiman de Pisarev et al. 1995; Li et al. 1989; Linko et al. 1986; Lissner et al. 1975; Mehendale et al. 1975; Rajamanickam and Padmanaban 1974; Smith et al. 1985; Wada et al. 1968).

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Agency Contact (Chemical Manager): Dr. Jessilynn Taylor



## APPENDIX B

### USER'S GUIDE

#### Chapter 1

##### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

#### Chapter 2

##### Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

## APPENDIX B

**Interpretation of Minimal Risk Levels**

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

**Chapter 3****Health Effects****Tables and Figures for Levels of Significant Exposure (LSE)**

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

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The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**LEGEND****See LSE Table 3-1**

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).
- (5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

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- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Figure 3-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.



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- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

**SAMPLE**

**Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

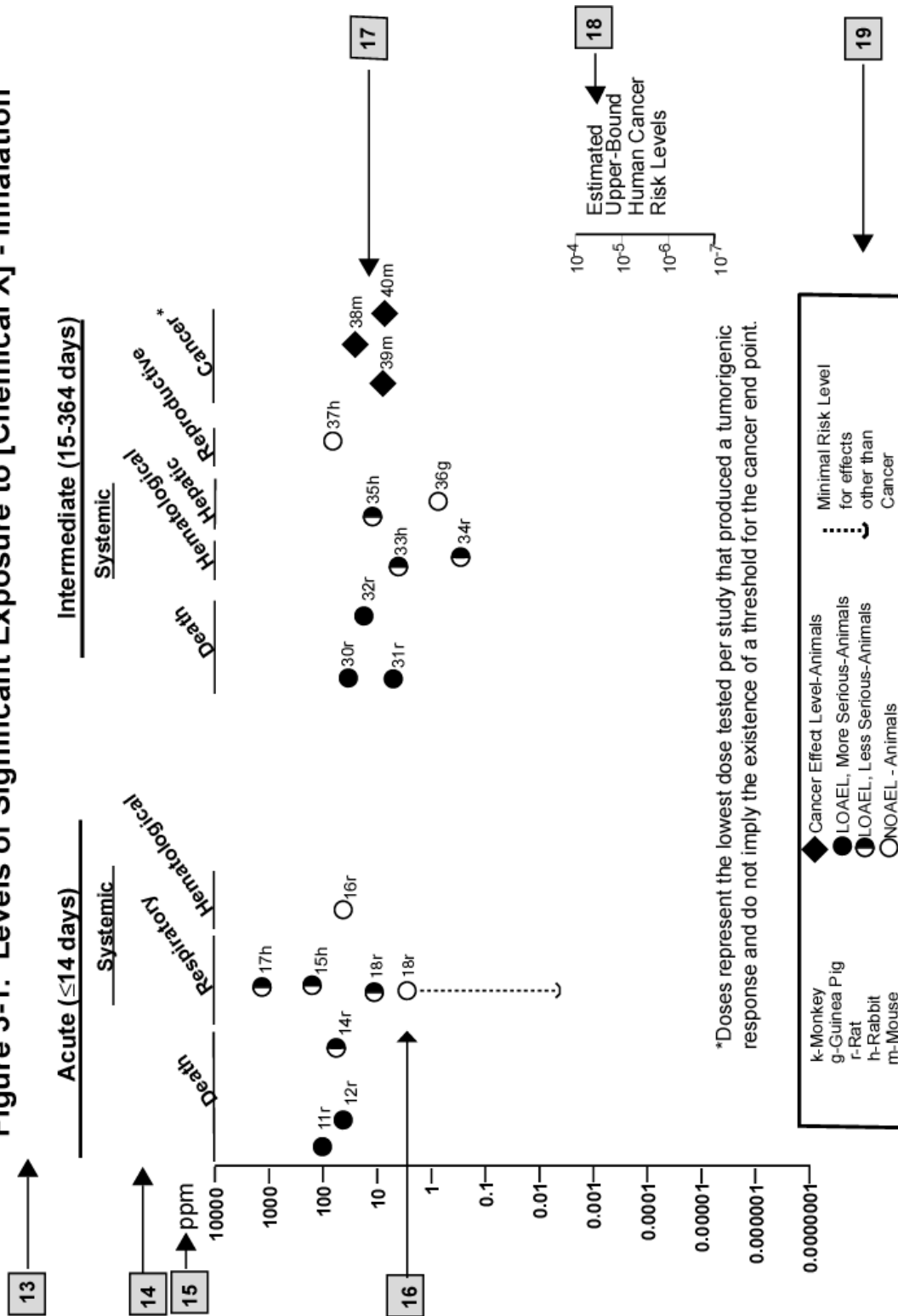
Key to figure <sup>a</sup>	Species	Exposure frequency/duration	System	LOAEL (effect)			Reference
				NOAEL (ppm)	Less serious (ppm)	Serious (ppm)	
1							
<b>INTERMEDIATE EXPOSURE</b>							
2	5	9	7	8	9	10	
3	9	9	9	9	9	9	
4	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)		Nitschke et al. 1981
<b>CHRONIC EXPOSURE</b>							
						11	
Cancer	Rat	18 mo 5 d/wk 7 hr/d				9	Wong et al. 1982
38						20	(CEL, multiple organs)
39	Rat	89–104 wk 5 d/wk 6 hr/d				10	(CEL, lung tumors, nasal tumors) NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d				10	(CEL, lung tumors, hemangiosarcomas) NTP 1982

<sup>a</sup> The number corresponds to entries in Figure 3-1.

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

**Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation**





## APPENDIX C

### ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

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DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F <sub>1</sub>	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	<i>Federal Register</i>
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K <sub>d</sub>	adsorption ratio
kg	kilogram
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration, low
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LD <sub>50</sub>	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	lutinizing hormone
LT <sub>50</sub>	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

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MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic

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PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to



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%	percent
$\alpha$	alpha
$\beta$	beta
$\gamma$	gamma
$\delta$	delta
$\mu\text{m}$	micrometer
$\mu\text{g}$	microgram
$q_1^*$	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result



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