

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.

MINIMAL RISK LEVEL WORKSHEET

Chemical name: Polybrominated Biphenyls (PBBs)
 CAS number(s): 36355-01-8 (unspecified hexabromo mixture)
 Date: September 2002
 Profile status: Draft for Public Comment
 Route: Inhalation Oral
 Duration: Acute Intermediate Chronic
 Key to figure: 3
 Species: Rat

MRL: 0.01 mg/kg/day ppm mg/m³

Reference: Allen-Rowlands CF, Castracane VD, Hamilton MG, et al. 1981. Effect of polybrominated biphenyls (PBB) on the pituitary - thyroid axis of the rat. Proc Soc Exp Biol Med 166:506-514.

Experimental design: Groups of 8–11 male rats were treated with 0, 1, 3, or 6 mg/kg/day doses of an unspecified mixture of PBBs in lecithin liposomes by gavage for 10 days. Plasma T₄ was assayed on treatment days 10 and 20. Other end points were evaluated on treatment day 20; these included plasma TSH levels, 5-hour thyroid uptake of ¹³¹I, incorporation of ¹³¹I into monoiodotyrosine, diiodotyrosine, T₃ or T₄, amount of intrathyroidal iodide, thyroid and liver weights, and body weights. Differences between mean values for the measured parameters in the control and PBB-treated groups were analyzed with the Student's *t*-test, with a *P* value of 0.05 considered as statistically significant.

Effects noted in study and corresponding doses: Plasma (T₄) was significantly (p<0.05) decreased at \$3 mg/kg/day after 10 and 20 days; this reduction was both dose and time-dependent. Plasma TSH levels were significantly elevated (p<0.01) at 6 mg/kg/day. The 6 mg/kg dose also produced a significant increase (p<0.01) in the 5-hour thyroid uptake of ¹³¹I and a significant depression (p<0.01) in the incorporation of ¹³¹I into monoiodotyrosine, without any apparent effect on the incorporation of ¹³¹I into diiodotyrosine, T₃ or T₄. There was a significant increase (p<0.01) of intrathyroidal iodide (nine rats/dose evaluated). At \$3 mg/kg, the absolute thyroid weights were significantly increased (p<0.01) (not evaluated at 1 mg/kg). Relative liver weight was significantly increased at \$1 mg/kg/day, but no treatment related effects on body weight were observed. The 1 mg/kg/day dose is considered a NOAEL.

Dose and end point used for MRL derivation:

NOAEL LOAEL

Uncertainty factors used in MRL derivation:

10 for extrapolation from animals to humans
 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? NA

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

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Other additional studies or pertinent information that lend support to this MRL: It is well documented in intermediate-duration studies that the thyroid is a target of PBBs showing a spectrum of effects, including decreases in serum T₃ and T₄ hormone, thyroid enlargement, effects in the follicular cells (e.g., reduced size, hyperplasia with columnar appearance, and papillary projections) and accumulation of colloid droplets (Akoso et al. 1982; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978; Norris et al. 1975; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978).

Agency Contact (Chemical Manager): Dr. Hana Pohl

MINIMAL RISK LEVEL WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
CAS number(s): 32534-81-9 (pentaBDE), 32536-52-0 (octaBDE), 1163-19-5 (decaBDE)
Date: September 2002
Profile status: Draft for Public Comment
Route: [] Inhalation [X] Oral
Duration: [X] Acute [] Intermediate [] Chronic
Key to figure: 34
Species: Rat

MRL: 0.03 [X] mg/kg/day [] ppm [] mg/m³

Reference: Zhou T, Taylor MM, DeVito MJ, et al. 2002. Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption. *Toxicol Sci* 66:105-116.

Experimental design: Groups of 47, 47, 55, and 55 primiparous Long-Evans rats were administered a technical pentaBDE mixture (DE-71) in corn oil by gavage from gestation day (Gd) 6 through postnatal day (Pnd) 21, except for Pnd 0 (day of birth). DE-71 is a technical mixture consisting primarily of tetra and penta congeners. Dams were sacrificed on Gd 20 and Pnd 22 and offspring were sacrificed on Gd 20 and Pnds 4, 14, 36, and 90). Serum and liver samples were obtained from a minimum of eight litters at each age point and analyzed for thyroid hormone (total T₄ and T₃) concentrations, liver weight, and hepatic microsomal enzyme (EROD, PROD, UDPGT) activities. Serum T₃ was not assayed in Gd 20 fetuses due to insufficient serum sample volume. Other study end points included number of pups delivered on Gd 21, number and sex of pups on Pnds 4, 7, 14, and 21, body weight of pups on Pnds 4, 7, 14, 21, 36, and 90, eye opening status (pups with at least one eye open) on Pnds 11–18, and maternal body weight on Gd 6 through Pnd 21.

The litter was the statistical unit for all analyses. Analysis of variance (ANOVA) was used to analyze for effects of treatment and interactions. If there was more than one independent variable, significant interactions were followed by step-down ANOVA tests for each independent variable (e.g., treatment and age). A nested design was used when more than one reading for each litter was obtained (e.g., body weights for males and females from the same litter). Repeated-measure ANOVAs were applied to data on dam body weights, preweaning offspring body weights (Pnds 4–21), and eye opening. Postweaning offspring body weights (Pnds 36–91) were analyzed with a two-way ANOVA, with time and dose as independent variables and litter nested under treatment. For significant effects of treatment, Duncan's Multiple Comparison test was used for mean contrast comparisons. The fetal T₄ data were analyzed with the Kruskal-Wallis test followed by a Dunn Multiple Comparison tests (due to a lack of homogeneity of variance). A significance level of 0.05 was used for all statistical tests. Benchmark dose estimates were determined for alterations in thyroid hormones and hepatic enzyme activity using the U.S. EPA Benchmark Dose Software (BMDS, V 1.3).

Effects noted in study and corresponding doses: No treatment-related effects on gestation length, litter size, sex ratio, viability index (percent of pups surviving until day 4), maternal or offspring body weights, or offspring eye opening were observed. The perinatal maternal exposure to PentaPBE caused significant ($p < 0.05$) decreases in serum total T₄ in dams at 30 mg/kg/day on Gd 20 and Pnd 22 (48 and 44%, respectively, relative to controls), and in fetuses and offspring at 10 mg/kg/day on Gd 20 (at least 15% reduced) and Pnds 4 and 14 (50 and 64% maximal in the 10 and 30 mg/kg/day groups, respectively). The effect on T₄ concentrations in offspring was age-dependent as values returned to control levels by Pnd 36. There were no exposure-related effects on serum total T₃ concentrations at any time in the dams or offspring. Relative liver weight was significantly ($p < 0.05$) increased in dams from Gd 20 to Pnd 22

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(approximately 8% above controls) at 30 mg/kg/day and offspring during the early preweaning period at \$10 mg/kg/day. Liver weights in offspring were maximal at 30 mg/kg/day on Pnds 4 and 14 (35 and 39% above controls, respectively) and returned to control levels by Pnd 36. Microsomal enzyme activity was increased in both dams and offspring as shown by significantly elevated hepatic EROD and PROD at \$10 mg/kg/day in dams on Gd 20 and Pnd 22 and offspring on Gd 20 and Pnds 4, 14, and 36, and significantly elevated UDPGT at 30 mg/kg/day in dams on Gd 20 and Pnd 22 and offspring on Gd 20 and Pnds 4 and 14. Benchmark dose analysis of the data found that the BMD and BMDL (95% lower confidence bound confidence limit on the effective dose) resulting in a 20% reduction of serum T₄ (LED₂₀) were 2.36 and 0.94 mg/kg/day, respectively. The respective BMD and BMDL resulting in 50% increased enzyme activity were 0.43 and 0.31 mg/kg/day for EROD, 0.48 and 0.36 mg/kg/day for PROD, and 5.50 and 3.41 mg/kg/day for UDPGT.

Dose and end point used for MRL derivation:

NOAEL [] LOAEL

A NOAEL of 1 mg/kg/day and a LOAEL of 10 mg/kg/day were identified for reduced serum T₄ levels in fetal rats on Gd 20.

Uncertainty factors used in MRL derivation:

10 for extrapolation from animals to humans
 3 for human variability

A component factor of 10 was not used for human variability because the MRL is based on effect levels identified in a sensitive subgroup (i.e., neonates exposed *in utero*).

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA (gavage study)

Was a conversion used from intermittent to continuous exposure? NA

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

Other additional studies or pertinent information that lend support to this MRL: The NOAEL of 1 mg/kg/day and LOAEL of 10 mg/kg/day for reduced serum T₄ hormone levels in fetal rats that were exposed to pentaBDE in the acute MRL study (Zhou et al. 2002) are supported by a NOAEL of 3 mg/kg/day and LOAEL of 10 mg/kg/day for reduced serum T₄ levels in weanling rats that were exposed to octaBDE for 4 days (Zhou et al. 2001). Thyroid hormone levels were determined in groups of eight weanling (28-day-old) female Long-Evans that were treated by gavage for 4 days with commercial mixtures of decaBDE (DE-83R) or octaBDE (DE-79) in doses of 0.3, 1, 3, 10, 30, 60, or 100 mg/kg/day, or pentaBDE (DE-71) in doses of 0.3, 1, 3, 10, 30, 100, or 300 mg/kg/day. The animals were sacrificed on the day after the last exposure and evaluated for changes in serum total T₄, total T₃, and TSH, hepatic microsomal EROD, PROD, and UDPGT activities, and body and liver weight. No dose-related effects on any of the measured parameters were observed for decaBDE. OctaBDE and pentaBDE caused reduced thyroid hormone levels and increased microsomal enzyme activities.

Effects of octaBDE included dose-related reductions in serum total T₄ levels with statistically significant (p<0.05) decreases occurring at \$10 mg/kg/day and a 70% maximum decrease compared to controls at 100 mg/kg/day (Zhou et al. 2001). Serum T₃ levels were reduced less than T₄ levels and were significant at \$60 mg/kg/day with a maximum reduction of 25% at the highest dose of 100 mg/kg/day. There were no exposure-related changes in serum total TSH concentrations. Hepatic microsomal EROD and UDPGT

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activities and relative liver weight were significantly ($p < 0.05$) increased at \$30 mg/kg/day and PROD activity was increased at \$10 mg/kg/day in dose-related responses. No treatment-related effects on body weight or visible signs of toxicity were observed. Benchmark dose analysis of the octaBDE data found that the BMD and BMDL resulting in a 20% reduction in thyroid hormones (LED_{20}) were 9.25 and 5.29 mg/kg/day, respectively, for serum T_4 and 53.38 and 11.98 mg/kg/day, respectively, for serum T_3 . The respective BMD and BMDL resulting in 50% increased enzyme activity were 3.66 and 2.45 mg/kg/day for EROD, 0.53 and 0.40 mg/kg/day for PROD, and 21.17 and 11.03 mg/kg/day for UDPGT.

Effects of pentaBDE included dose-related reductions in serum total T_4 levels with significant ($p < 0.05$) decreases occurring at \$30 mg/kg/day and an 80% maximum decrease compared to controls 300 mg/kg/day (Zhou et al. 2001). Serum total T_3 levels were reduced less than T_4 levels and were significant at \$100 mg/kg/day with a maximum reduction of 30% at the highest dose of 300 mg/kg/day. There were no exposure-related changes in serum total TSH concentrations. Hepatic microsomal EROD and PROD activities and relative liver weight were significantly ($p < 0.05$) increased at \$10 mg/kg/day and UDPGT activity was increased at \$30 mg/kg/day in dose-related responses. No treatment-related effects on body weight or visible signs of toxicity were observed. The BMD and BMDL resulting in a 20% reduction in thyroid hormones (LED_{20}) were 12.74 and 6.95 mg/kg/day, respectively, for serum T_4 and 32.94 and 8.56, respectively, mg/kg/day for serum T_3 . The respective BMD and BMDL resulting in 50% increased enzyme activity were 2.88 and 1.82 mg/kg/day for EROD, 0.81 and 0.54 mg/kg/day for PROD, and 9.51 and 5.83 mg/kg/day for UDPGT.

Thyroid effects that mainly included reduced serum T_4 hormone levels and follicular cell hyperplasia have been observed in a number of other studies of PBDEs in orally-exposed animals. Other acute-duration studies showed decreases in serum T_4 in rats and mice exposed to \$18 mg/kg/day pentaBDE for 14 days (Fowles et al. 1994; Hallgren et al. 2001). Effects observed in intermediate-duration studies include thyroid hyperplasia in rats exposed to \$8 mg/kg/day octaBDE for 30 days (Norris et al. 1973, 1975) and reduced serum T_4 in rats exposed to \$10 mg/kg/day pentaBDE for 90 days (WIL Research Laboratories 1984). Intermediate-duration exposure to a 77% decaBDE/22% nonaBDE commercial mixture caused thyroid hyperplasia in rats at doses \$80 mg/kg/day for 30 days (Norris et al. 1973, 1975). Chronic (103-week) exposure to high-purity decaBDE (\$97%) did not induce thyroid histopathological changes in rats at #2,550 mg/kg/day, although follicular cell hyperplasia developed in mice exposed to 2,240 mg/kg/day (NTP 1986).

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MINIMAL RISK LEVEL WORKSHEET

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CAS number(s): 32534-81-9 (pentaBDE), 32536-52-0 (octaBDE), 1163-19-5 (decaBDE)
Date: September 2002
Profile status: Draft for Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Key to figure: 47
Species: Rat
MRL: 0.007 mg/kg/day ppm mg/m³

Reference: WIL Research Laboratories. 1984. 90-day dietary study in rats with pentabromodiphenyl oxide (DE-7) (Volume I-II). Submitted to U.S. EPA under TSCA Section 8D, Fiche no. OTS0524336.

Experimental design: PentaBDE (commercial mixture DE-71) was administered to Sprague-Dawley rats in the diet at dosage levels of 0, 2, 10, or 100 mg/kg/day for 90 days. Ten rats/sex/group were sacrificed after 4 weeks, 10 rats/sex/group were sacrificed at the end of the 90-day exposure period, and the remaining rats were sacrificed after a 6-week recovery period (5 rats/sex/group) or 24-week recovery period (5 rats/sex/group). Animals were observed daily for general appearance, behavior, signs of overt toxicity, and mortality during the dosing and recovery periods. Body weight and food consumption were measured during the dosing period and the first 4 weeks of the recovery period. Hematology, clinical chemistry (including serum T₃ and T₄), and urinalysis parameters, urine and liver porphyrin levels, and serum bromide levels were evaluated in 10 rats/sex/group at weeks 4 and 13. Bromine levels in liver, lung, kidney, thymus, and thyroid were evaluated at weeks 4, 13, 19, and 37. Gross necropsies and organ weight measurements (brain, gonads, heart, liver, kidneys, thymus, and thyroid) were performed on all rats. Histological examinations included liver, lung, kidney, thymus, thyroid, and gross lesions in all dose groups at the week 4, 13, 19, and 37 sacrifices and in all tissues (comprehensive evaluation) in the 0 and 100 mg/kg/day groups.

All statistical analyses were conducted using two-tailed tests for a minimum significance level of 5% comparing treatment groups to the controls. Analysis of weekly body weights, body weight changes, food consumption, clinical laboratory values, and absolute and relative organ weights were analyzed by a one-way analysis of variance and Dunnett's Test. The one-tailed Kolmogorov-Smirnov test was used for the 4- and 13-week histopathological diagnoses.

Effects noted in study and corresponding doses: Effects observed were observed at \$2 mg/kg/day and included histological changes in the liver after 4 and 13 weeks of exposure as well as increased bromine levels in essentially all measured tissues. Hepatocytomegaly occurred in males at 2 mg/kg/day and both sexes were affected at the higher doses. Incidences of hepatomegaly in the control to high dose groups at 13 weeks were 0/10, 7/10, 10/10, and 10/10 in males and 0/10, 0/10, 8/10, and 10/10 (statistical tests not conducted) in females. Some hepatocytes in affected areas had vacuoles, which were empty in tissue sections and reportedly likely contained neutral lipid. Incidences of hepatocyte vacuolation at 13 weeks were 2/10, 4/10, 3/10, and 2/10 in males and 3/10, 5/10, 5/10, and 6/10 in females. The hepatocytomegaly was similar in incidence and severity after 4 and 13 weeks, appeared to be dose-related with respect to severity, and was not completely reversible as it was still observed in males at \$10 mg/kg/day and in females at 100 mg/kg/day at 24 weeks postexposure in lessened severity and incidence. Females in the 2 and 100 mg/kg/day groups appeared to have an increased incidence of degeneration and necrosis of individual liver parenchymal cells at 24 weeks postexposure; the investigators concluded that this condition may represent the final loss of previously damaged cells and probably should be considered compound-related. Incidences of individual liver cell

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degeneration/necrosis in the female control to high dose groups at 24 weeks postexposure were 2/5, 5/5, 2/5, and 5/5. Small increases in thyroid hyperplasia appeared to occur in lower dose groups; incidences in the control to high dose groups at 13 weeks were 0/10, 2/10, 2/10, and 5/10 in males and 0/10, 0/10, 1/10, and 4/10 in females. The thyroid hyperplasia was very slight in severity at 2 and 10 mg/kg/day, very slight to slight severity at 100 mg/kg/day, and reversible in that it was no longer observed at 24 weeks postexposure in any animals; the thyroid changes therefore were mild and transient. Serum T₄ levels were significantly reduced in both sexes at \$10 mg/kg/day, indicating that 10 mg/kg/day is the LOAEL for thyroid effects. The slight thyroid hyperplasia and reductions in plasma T₄ levels are likely indirect consequences of hepatic enzyme induction. No compound-related changes were observed in any tissues other than the liver and thyroid at any dose level. Other effects observed at \$10 mg/kg/day included increased serum bromide levels in both sexes at 4 weeks (only increased in both sexes at 100 mg/kg/day at 13 weeks), and increased urine porphyrins in both sexes and liver porphyrins in females (liver porphyrins increased in males at 100 mg/kg/day). Effects observed at 100 mg/kg/day included decreased body weight gain in both sexes, decreased food consumption in females, and increased serum cholesterol in both sexes at weeks 4 and 13, and increased absolute and relative liver weights in both sexes at 13 weeks (returned to normal ranges after 24 weeks of recovery).

Dose and end point used for MRL derivation:

[] NOAEL [X] LOAEL

The lowest tested dose, 2 mg/kg/day, is a minimal LOAEL for hepatic effects (hypertrophy, mild degeneration, and slight necrosis).

Uncertainty factors used in MRL derivation:

- [X] 3 for extrapolation from a minimal LOAEL to a NOAEL
- [X] 10 for extrapolation from animals to humans
- [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No (reported doses)

Was a conversion used from intermittent to continuous exposure? NA.

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

Other additional studies or pertinent information that lend support to this MRL: The hepatotoxic potential of PBDE mixtures is well-documented in animals by oral exposure. The spectrum of observed hepatic effects includes microsomal enzyme induction, liver enlargement, and degenerative histopathologic alterations that progress to tumors. Repeated dietary exposure to PBDEs typically caused liver enlargement with or without degenerative changes, and effects were generally dose-related in incidence and severity, more frequent and pronounced in males than females, and more severe with octaBDE and pentaBDE than decaBDE. Hepatic effects induced by chronic exposure to decaBDE included degeneration and thrombosis in rats exposed to 2,240 mg/kg/day and centrilobular hypertrophy and granulomas in mice exposed to \$3,200 mg/kg/day (NTP 1986). Data from other intermediate-duration studies that support selection of the 2 mg/kg/day critical LOAEL include hepatic LOAELs of 5 mg/kg/day for cytomegaly (with vacuolation and necrosis at higher doses) in rats exposed to octaBDE for 13 weeks (IRDC 1977), 8 mg/kg/day for hepatocellular enlargement and vacuolation in rats exposed to octaBDE for 30 days (Norris et al. 1973, 1975), and 9 mg/kg/day for hepatocellular enlargement and increased liver weight in rats exposed to octaBDE or pentaBDE for 28 days (IRDC 1976).

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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.

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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/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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

1 6

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

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
INTERMEDIATE EXPOSURE							
2 6	5	6	7	8	9		10
3 6	Systemic	9	9	9	9		9
4 6	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 ^b	10 (hyperplasia)	Nitschke et al. 1981
CHRONIC EXPOSURE							
						11	
	Cancer					9	
38	Rat	18 mo 5 d/wk 7 hr/d				20	(CEL, multiple organs) Wong et al. 1982
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

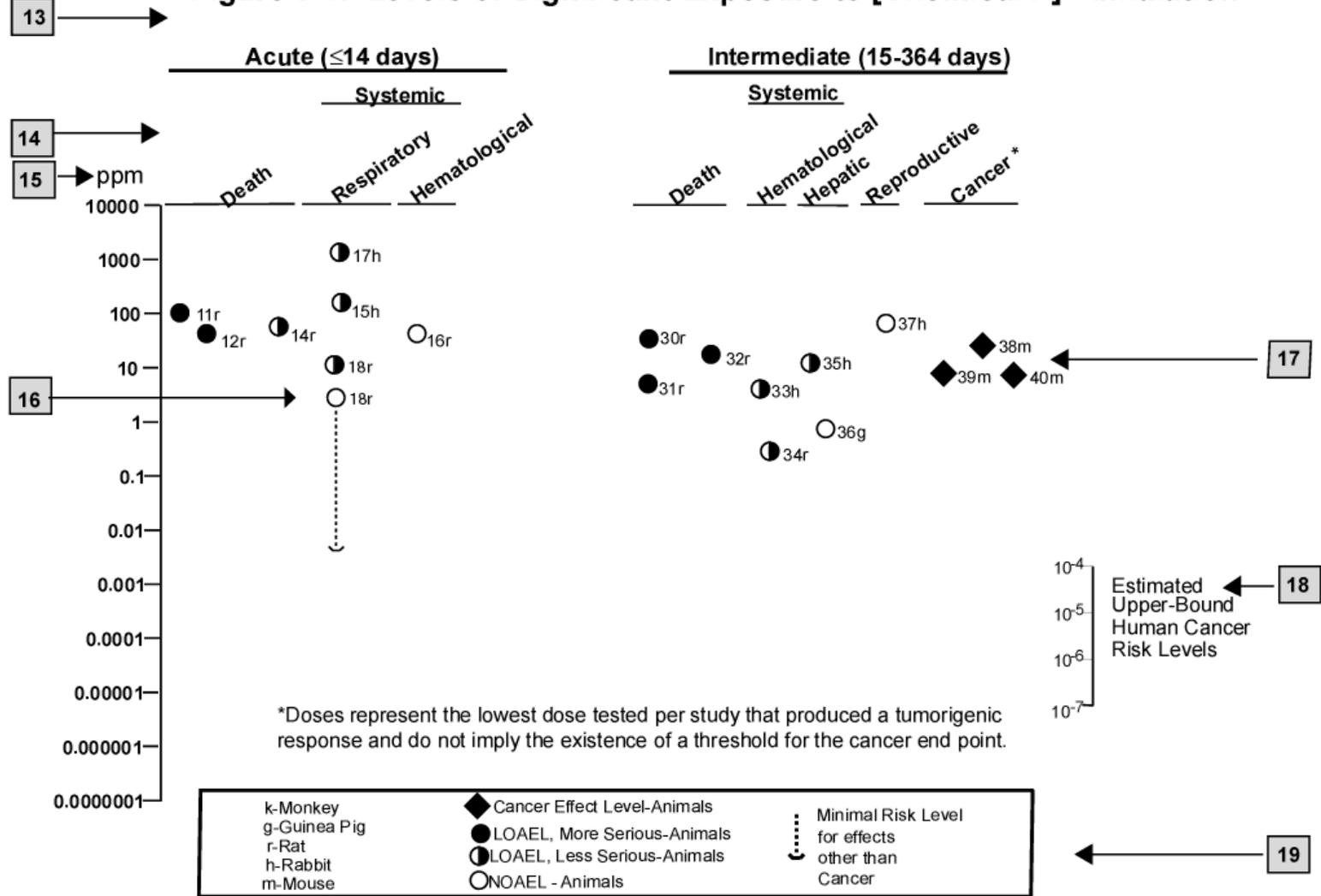
^a The number corresponds to entries in Figure 3-1.

12 6

^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-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).

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



DRAFT FOR PUBLIC COMMENT

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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 ₁	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 _d	adsorption ratio
kg	kilogram
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration, low
LC ₅₀	lethal concentration, 50% kill
LD _{Lo}	lethal dose, low
LD ₅₀	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	lutinizing hormone
LT ₅₀	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
Pnd	postnatal day
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 ₅₀	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

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<	less than
#	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result

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