APPENDIX A. ATSDR MINIMAL RISK LEVELS 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.

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 100-fold 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 agency-wide 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 NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
[Lower Brominated Diphenyl Ethers]
CAS number(s): 32534-81-9 (pentaBDE), 32536-52-0 (octaBDE)
Date: September 2, 2004
Profile status: Final Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 3
Species: Rat

Minimal Risk Level: 0.006 [ ] mg/kg/day [ ] ppm [X] mg/m^3

Reference: Great Lakes Chemical Corporation. 2000. A 90-day inhalation toxicity study of octabromodiphenyl oxide in albino rats, dated 04/04/02. Submitted to the U.S. EPA under TCSA Section 8E, Fiche no. OTS0574171-1.

Experimental design: This is an unpublished industry-sponsored study in which a commercial octaBDE product (Lot No. 9525DA23B, bromine content 78.7%, composition and purity not otherwise specified) was administered to groups of 10 male and 10 female Crl:CD(SD)IGS BR rats, via nose-only inhalation as a dust aerosol, in measured concentrations of 0 (filtered air-only), 1.1, 16 or 202 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks. The mean MMADs in the low to high level groups were 2.0, 2.7, and 2.8 microns; the corresponding mean GSDs were 3.37, 3.72, and 3.01. Clinical and physical signs, body weight, food consumption, and survival were evaluated throughout the study. Ophthalmic, hematology (11 indices), serum chemistry (18 indices), and serum thyroid hormone (TSH, total T_3, and total T_4) evaluations were performed near the end of the exposure period. Urinalyses were not conducted. Comprehensive necropies, organ weight measurements, and histological examinations (including respiratory tract and thyroids) were performed following exposure termination.

Effects noted in study and corresponding doses: Hepatic, nasal, lung, thyroid, and ovarian effects were observed. The liver was affected in both sexes as shown by dose-related increases in centrilobular hepatocellular hypertrophy at ≥16 mg/m^3 and liver weight (absolute and relative) at 202 mg/m^3. Total incidences of centrilobular hepatocellular hypertrophy in the 0, 1.1, 16, and 202 mg/m^3 groups were 1/10 (minimal), 0/10, 3/10 (all minimal), and 10/10 (6 minimal, 2 mild, 2 moderate) in males, and 0/10, 0/10, 3/10 (all minimal), and 6/10 (3 minimal, 3 mild) in females. Changes in nasal Goblet cells were increased at 202 mg/m^3, but showed no clear dose-related increasing trends for incidence and severity. Total incidences of Goblet cell hypertrophy (minimal or mild) were slightly increased in nasal level II of both sexes at ≥1.1 mg/m^3; incidences in 0, 1.1, 16, and 202 mg/m^3 exposure groups were 4/10 (all minimal), 9/10 (7 minimal, 2 mild), 6/10 (all minimal), and 10/10 (9 minimal, 1 mild) in males, and 2/10 (all minimal), 6/10 (all minimal), 4/10 (all minimal), and 8/10 (all minimal) in females. Goblet cell hypertrophy was also slightly increased in nasal level IV in males at 202 mg/m^3 (4/10, 0/10, 1/10, and 8/10, all minimal severity, not increased in females). Histological changes in the lungs included alveolar histiocytosis and chronic active inflammation that were only clearly induced at 202 mg/m^3. Total incidences of alveolar histiocytosis at 0, 1.1, 16, and 202 mg/m^3 were 3/10 (2 mild, 1 minimal), 5/10 (all minimal), 5/10 (all minimal), and 10/10 (5 minimal, 3 mild, 2 moderate) in males, and 0/10, 5/10 (all minimal), 2/10 (all minimal), and 10/10 (1 minimal, 7 mild, 2 moderate) in females. Corresponding total incidences of chronic active lung inflammation were 0/10, 0/10, 2/10 (both minimal), and 10/10 (5 minimal, 4 mild, 1 moderate) in males, and 0/10, 1/10 (minimal), 1/10 (minimal), and 10/10 (2 minimal, 5 mild, 3 moderate) in females. Gross lung changes also occurred in both sexes at 202 mg/m^3; these included lung firmness and white discoloration and/or enlargement in the bronchial

and/or mediastinal lymph nodes. The lymph node effects correlated with the histological finding of granulomatous inflammation. There were no exposure-related gross or histopathological changes in the spleen, bone marrow, thymus, or other tissues, including thyroid. Thyroid hormone assessments, however, showed exposure-related decreases in mean thyroxine (total T_4) at ≥16 mg/m^3 in both sexes, and increases in thyroid stimulating hormone (TSH) at ≥16 mg/m^3 in males and 202 mg/m^3 in females. The changes were usually statistically significant ($p<0.05$ or $p<0.01$) compared to controls and considered to be consistent with chemical-induced hypothyroidism. There were no serum T_3 changes. Qualitative histological evaluations of step sections of ovaries showed an absence of corpora lutea in 3/10 females at 202 mg/m^3, compared to 0/10 in the control and lower exposure groups. This 30% incidence was interpreted to be a treatment-related effect because an absence of corpora lutea was considered unusual in rats at 20 weeks of age.

Other findings included some hematological alterations in 202 mg/m^3 females that were not considered to be exposure-related (slightly increased mean activated partial thromboplastin time, and decreased mean MCH and MCHC without effects on RBC counts, hematocrit, or hemoglobin levels). Serum chemistry evaluations showed that cholesterol was significantly increased (39.8% less than controls, $p<0.01$) in 202 mg/m^3 females, but the magnitude of the elevation was not considered toxicologically significant. Some other statistically significant serum chemistry alterations (increased mean globulin and total protein, decreased albumin/globulin ratio) also occurred in the 202 mg/m^3 females, but were not considered exposure-related due to small magnitudes of changes and lack of similar findings in the males.

Dose and end point used for MRL derivation: 1.1 mg/m^3

[X] NOAEL [ ] LOAEL

Considering the unclear adversity of minimal severity Goblet cell hypertrophy, lack of clear dose-related increasing trends for incidence and severity of this nasal effect, identification of both a NOAEL (1.1 mg/m^3) and LOAEL (16 mg/m^3) for changes in thyroid hormones, and abundant evidence for thyroid effects of PBDEs in oral studies, the NOAEL for effects on thyroid hormones is the most appropriate basis for derivation of the MRL.

Uncertainty factors used in MRL derivation:

[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability
[X] 3 modifying factor for incomplete data base

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

Was a conversion used from intermittent to continuous exposure? The NOAEL was adjusted to continuous exposure as follows: 1.1 mg/m^3 x 6 hours/24 hours x 5 days/7 days = 0.196 mg/m^3

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: The human equivalent NOAEL ($NOAEL_{HEC}$) was calculated from the duration-adjusted NOAEL ($NOAEL_{ADJ}$) using EPA RfC methodology as follows:

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDDR = 0.196 \text{ mg/m}^3 \times 2.7 = 0.53 \text{ mg/m}^3$$

The regional deposited dose ratio (RDDR) for the extrathoracic (ET) region was used to extrapolate deposited doses in rats to deposited doses in humans. The following parameters were used to calculate

the RDDR of 2.7: mean particle size (MMAD) of 2.0 µm with a mean GSD (sigma g) of 3.37; default human body weight of 70 kg, and a default female F344 rat body weight of 180 g.

Based on these values, the MRL is derived as follows:

$$MRL = NOAEL_{HEC} \div (UF \times MF) = 0.53 \div (30 \times 3) = 0.006 \text{ mg/m}^3$$

Other additional studies or pertinent information that lend support to this MRL: This is the only intermediate-duration inhalation study of PBDEs.

The thyroid is a sensitive target of lower brominated BDEs in orally exposed animals. A NOAEL for reduced serum T_4 hormone levels in fetal rats that were exposed to pentaBDE (Zhou et al. 2002) was used as the basis for the acute oral MRL for lower brominated BDEs. This study is supported by findings of reduced serum T_4 levels in weanling rats that were acutely exposed to octaBDE and pentaBDE as neonates (Zhou et al. 2001). Thyroid effects that mainly included reduced serum T_4 hormone levels and follicular cell hyperplasia were observed in a number of other animal studies of acute- or intermediate-duration oral exposure to penta- and octaBDEs (Fowles et al. 1994; Hallgren et al. 2001; WIL Research Laboratories 1984).

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Polybrominated Biphenyls (PBBs)
CAS number(s): 36355-01-8 (unspecified hexabromo mixture)
Date: September 2, 2004
Profile status: Final Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 4
Species: Rat

Minimal Risk Level: 0.01 [X] 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 T_4 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 ^{131}I, incorporation of ^{131}I into monoiodotyrosine, diiodotyrosine, T_3 or T_4, 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 (T_4) 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 ^{131}I and a significant depression ($p<0.01$) in the incorporation of ^{131}I into monoiodotyrosine, without any apparent effect on the incorporation of ^{131}I into diiodotyrosine, T_3 or T_4. 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.

Despite the fact that the inappropriate statistical test (t-test, rather than an ANOVA with multiple comparison tests) was used to analyze these data, ATSDR is confident with the designation of the NOAEL and LOAEL values. The data in the manuscript are presented graphically, with animal numbers presented as a range (8–11 animals/group); thus, an ANOVA could not be performed from the published report. However, using the graphical data, the change in plasma T4 levels in the 3 mg/kg/day groups is clearly on the order of 20–30%, which represents a biologically significant change. As such, the identification of 3 mg/kg/day as a LOAEL, and 1 mg/kg/day as a NOAEL, is not contraindicated by the lack of appropriate statistical analysis.

Dose and end point used for MRL derivation:

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[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? 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: 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 T_3 and T_4 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. 1982a, 1982b; Byrne et al. 1987; Gupta and Moore 1979; Kasza et al. 1978a; Norris et al. 1975a, 1975b, 1975c; NTP 1983; Sepkovic and Byrne 1984; Sleight et al. 1978).

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
[Lower Brominated Diphenyl Ethers]
CAS number(s): 32534-81-9 (pentaBDE), 32536-52-0 (octaBDE)
Date: September 2, 2004
Profile status: Final Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to figure: 27
Species: Rat

Minimal Risk Level: 0.03 [X] mg/kg/day [ ] ppm [ ] mg/m^3

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 primparous 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 T_4 and T_3) concentrations, liver weight, and hepatic microsomal enzyme (EROD, PROD, UDPGT) activities. Serum T_3 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 T_4 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 T_4 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 T_4 concentrations in offspring was age-dependent as values returned to control levels by PND 36. There were no exposure-related effects on serum total T_3 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 (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 signficantly 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 T_4 (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:

[X] NOAEL [ ] LOAEL

A NOAEL of 1 mg/kg/day and a LOAEL of 10 mg/kg/day were identified for reduced serum T_4 levels in fetal rats on GD 20.

Uncertainty factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 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 T_4 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 T_4 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 T_4, total T_3, 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 T_4 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 T_3 levels were reduced less than T_4 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 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, mg/kg/day, respectively, 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, 1975b) 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, 1975b). 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).

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name:	Polybrominated Diphenyl Ethers (PBDEs) [Lower Brominated Diphenyl Ethers]
CAS number(s):	32534-81-9 (pentaBDE), 32536-52-0 (octaBDE)
Date:	September 2, 2004
Profile status:	Final Post Public Comment
Route:	[ ] Inhalation [X] Oral
Duration:	[ ] Acute [X] Intermediate [ ] Chronic
Key to figure:	36
Species:	Rat

Minimal Risk Level: 0.007 [X] mg/kg/day [ ] ppm [ ] mg/m^3

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 T_3 and T_4), 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 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 T_4 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 T_4 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, 1975b), and 9 mg/kg/day for hepatocellular enlargement and increased liver weight in rats exposed to octaBDE or pentaBDE for 28 days (IRDC 1976).

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name: Polybrominated Diphenyl Ethers (PBDEs)
[Decabromodiphenyl Ether (DecaBDPE)]
CAS number(s): 1163-19-5
Date: September 2, 2004
Profile status: Final Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 13
Species: Mouse

Minimal Risk Level: 10 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Hardy ML, Schroeder R, Biesemeier J, et al. 2002. Prenatal oral (gavage) developmental toxicity study of decabromodiphenyl oxide in rats. Int J Toxicol 21:83-91.

Experimental design: A commercial decaBDPE product (97.34% DBDPO, 2.66% nonaBDE/octaBDE) was administered to groups of 25 mated female Sprague-Dawley rats by gavage in corn oil in daily doses of 0, 100, 300, or 1,000 mg/kg/day on gestation days 0 through 19. Each female was sacrificed on gestation day 20 and necropsied. End points examined included maternal clinical observations, maternal body weight/weight gain and food consumption, maternal gravid uterine and liver weights, maternal gross lesions, total number of corpora lutea, uterine implantations, early and late resorptions, viable and nonviable fetuses, and fetal weight and sex. Fetuses were examined grossly (all fetuses), evaluated for skeletal/cartilaginous malformations and ossification variations (approximately half of each litter), and evaluated for visceral malformations (remaining fetuses). The experiment was designed to meet current (as of 2002) EPA/OPPTS and OECD guidelines for a prenatal developmental toxicity study.

Effects noted in study and corresponding doses: No effects on any maternal end points (e.g., clinical signs, body weight, pregnancy rate, implantation, liver weight, necropsy findings) or fetal endpoints (e.g., body weight, sex ratio, or external, visceral or skeletal malformations) were observed in any dose group.

Dose and end point used for MRL derivation: 1,000 mg/kg/day

[X] NOAEL [ ] LOAEL

No exposure-related maternal or developmental toxicity was found, indicating that the critical NOAEL is 1,000 mg/kg/day, the highest tested dose.

Uncertainty factors used in MRL derivation:

[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? NA

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: One intermediate-duration oral systemic toxicity study of a high purity decaBDE commercial product was conducted. A commercial decaBDE mixture (94–97% pure) was fed to F344 rats (10/sex/level) and B6C3F1 mice (10/sex/level) in dietary concentrations of 0, 3,100, 6,300, 12,500, 25,000, or 50,000 ppm for 13 weeks (NTP 1986). Corresponding estimated daily doses are 0, 496, 992, 2,000, 4,000, or 8,000 mg/kg/day in rats, and 0, 589, 1,178, 2,375, 4,750, or 9,500 mg/kg/day in mice. The daily doses (mg/kg body weight/day) were estimated by multiplying the dietary concentrations (ppm; mg/kg food) by food factors of 0.16 kg food/kg body weight/day for rats and 0.19 kg food/kg body weight/day for mice. The food factors are based on the averages of male and female subchronic reference values for food consumption and body weight in F344 rats and B6C3F1 mice (EPA 1988a). All animals were observed daily, weighed weekly, and necropsied at the end of the exposure period. Comprehensive histological examinations were also performed at the end of the study, but were limited to the control and high-dose groups. No compound-related clinical signs, deaths, body weight or food consumption changes, gross pathology, or histopathology were observed in either species at any level of exposure.

Based on the findings of the NTP (1986) study, the intermediate-duration NOAELs for systemic toxicity are 8,000 mg/kg/day in rats and 9,500 mg/kg/day in mice. The NOAEL for developmental toxicity is 1,000 mg/kg/day (Hardy et al. 2002). Because doses higher than 1,000 mg/kg/day have not been tested for developmental toxicity, and the NTP (1986) study indicates that this dose is also a NOAEL for systemic toxicity, the 1,000 mg/kg/day developmental toxicity NOAEL is used as the basis for the MRL.

Agency Contact (Chemical Manager): Dr. Hana Pohl

APPENDIX B. USER'S GUIDE

Chapters 1 and 2

Public Health Statement

These chapters of the profile are health effects summaries written in non-technical language. Their intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statements 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 Statements 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.

Chapters 3 and 4

Relevance to Public Health

These chapters provide health effects summaries based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. These summaries are 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 chapters cover end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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.

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 5 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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.

MRLs 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. Chapters 3 and 4, "Relevance to Public Health," contain basic information known about the substance. Other sections such as Chapter 5 Section 5.9, "Interactions with Other Substances," and Section 5.10, "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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

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 no-observed-adverse-effect level (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 levels of significant exposure (LSE) Tables.

Chapter 5

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 5-1 and Figure 5-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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. Typically 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 5-1, 5-2, and 5-3, respectively). LSE figures are limited to the inhalation (LSE Figure 5-1) and oral (LSE Figure 5-2) 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 two "18r" data points in sample Figure 5-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapters 3 and 4, "Relevance to Public Health," cover the relevance of animal data to human toxicity and Section 5.4, "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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 11 of the profile.

(11) CEL. A 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 5-1 (page B-7)

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 acute and intermediate 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^3 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 one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(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 → **TABLE 5-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
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

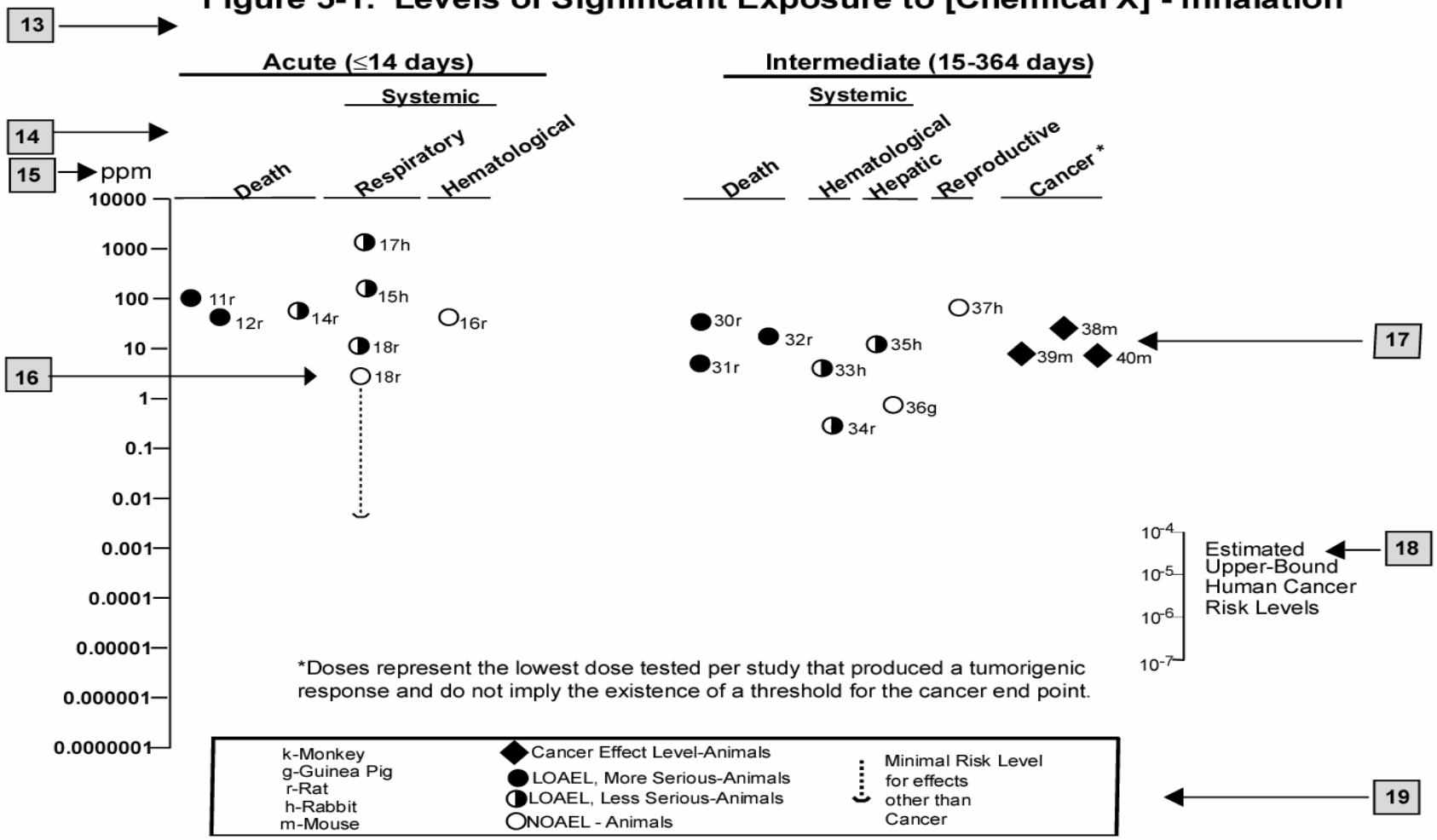
12 →

[a] The number corresponds to entries in Figure 5-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ 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 5-1. Levels of Significant Exposure to [Chemical X] - Inhalation



APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
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
AOEC	Association of Occupational and Environmental Clinics
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
BMD	benchmark dose
BMR	benchmark response
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

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	Federal Register
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
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
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
NHANES	National Health and Nutrition Examination Survey
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
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
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
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
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
<	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

APPENDIX D. INDEX

APPENDIX D