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. 99-4991, 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 (MRL) WORKSHEET

Chemical name(s): Hexachlorocyclopentadiene
CAS number(s): 77-47-4
Date: January 15, 1999
Profile status: Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 44
Species: rat

MRL: 0.01 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Rand GM, Nees PO, Calo CJ, et al. 1982b. The Clara cell. An electron microscopy examination of the terminal bronchioles of rats and monkeys following inhalation of hexachlorocyclopentadiene. J Toxicol Environ Health 10:59-72.

Experimental design: Groups of Sprague-Dawley rats (3/dose) were exposed to HCCPD vapors for up to 14 weeks (6 hours/day, 5 days/week). Doses of 0.01, 0.05, and 0.2 ppm were used. Following exposure, animals were sacrificed and lung tissue prepared for histological examination using light and electron microscopy. No other parameters were measured.

Effects noted in study and corresponding doses: A statistically significant ($p<0.01$) dose-related increase in the number of electron-lucent inclusions in Clara cells in the lungs was reported at all exposure levels following electron microscopic examination. Light microscopy did not reveal treatment-related histopathological lesions of the lungs.

Dose and endpoint used for MRL derivation: A concentration of 0.2 ppm was used to derive the MRL, based on the presence of effects on the Clara cells of the lungs. Clara cells are nonciliated epithelial cells located in the terminal bronchiole region. The response of the Clara cells was considered to be an adaptive response to the exposure to inhaled toxicants, since Clara cells contain mixed function oxidases and are responsible for detoxifying inhaled chemicals. Thus, Clara cells are biomarkers of exposure, and not effect. This concentration was not normalized due to the chemical activity of HCCPD and its tendency to form lesions in directly exposed tissues.

[X] NOAEL [] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a minimally adverse LOAEL)
[ ] 1 [X] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

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

The intermediate inhalation MRL for HCCPD is derived as follows.

$VE_A = (0.25\ m^3/d)^a \times (1000\ L/m^3) \times (1d/24\ hr) \times (1\ hr/60\ min) \times (1000\ mL/L) = 170\ mL/min$

$VE_H = (20\ m^3/d)^b \times (1000\ L/m^3) \times (1d/24\ hr) \times (1\ hr/60\ min) \times (1000\ mL/L) = 13800\ mL/min$

$RGDR_{[PU]}{}^c = (VE/SA_{PU})_A/(VE/SA_{PU})_H = (170\ mL/min/0.34\ m^3)/(13800\ mL/min/54\ m^3) = 1.95$

$NOAEL_{HEC} = NOAEL \times RGDR = 0.2\ ppm \times 1.95 = 0.39\ ppm$

$MRL = NOAEL_{HEC} \div UF$

$MRL = 0.4\ ppm \div 30$

$MRL = 0.01\ ppm$

[a]Average inhalation rate for male and female Sprague-Dawley rats for subchronic duration.
[b]Average inhalation rate for humans.
[c]Derived from equation 4-28 of EPA 1994 (EPA/600/8-90-066F).

Was a conversion used from intermittent to continuous exposure? No. A conversion factor was not used to adjust for intermittent exposure due to the corrosive nature of HCCPD. The chemical exerts a direct contact effect, and the effects are concentration- rather than time-dependent.

Other additional studies or pertinent information that lend support to this MRL: Treon JR, Cleveland FP, Cappel J, et al. 1955. The toxicity of hexachlorocyclopentadiene. Arch Ind Health 11:459-472.

Groups of mice (5), guinea pigs (2), rats (4), and rabbits (3) were exposed to vapors of HCCPD (0.13 ppm, 7 hours/day, 5 days/week, generated from 89.5% pure HCCPD) for 30 weeks. Following exposure, clinical signs and survival were monitored. Gross necropsy was performed. Pulmonary edema and bronchitis were reported in mice. Compound exposure was associated with pneumonia in rats and guinea pigs. Comparable effects were not seen in rabbits survival was not affected following compound exposure in rabbits, rats, and guinea pigs. On the other hand, mice were more sensitive to HCCPD toxicity, with death occurring in 4 of 5 mice.

Rand GM, Nees PO, Calo CJ, et al. 1982a. Effects of inhalation exposure to hexachlorocyclopentadiene on rats and monkeys. J Toxicol Environ Health 9:743-760.

Groups of Sprague-Dawley rats (40/sex/dose) were exposed to vapors of HCCPD at concentrations of 0, 0.01, 0.05, or 0.20 ppm for 90 days (up to 14 weeks) (6 hours/day, 5 days/week). Following exposure, clinical signs, food and water consumption were monitored daily, and body weights were recorded weekly during the treatment period. Standard blood chemistry, hematologic, and urinalysis parameters were evaluated. Gross necropsy was performed and organ weights (adrenal, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thyroid, and uterus) were determined. Histopathological examinations of major organs were performed at 4, 8, and after 13 weeks in the control and high-dose groups. There was a slight marginal increase in hemoglobin, red blood cell count, and mean corpuscular hemoglobin concentration and a decrease in mean cell volume at concentrations of 0.01 (males), 0.05 (females), and 0.2 (both sexes) ppm after 12 weeks exposure to the compound. These changes may represent a compensatory response to impaired oxygen transport and thus provide some support for impaired lung function. Adverse clinical signs (dark red eyes) were evident at concentrations of 0.05 pm or greater; however, these effects were reversible after day 20 of the 90-day exposure period. Liver weights were reduced in both sexes at all exposure levels, and kidney weights were reduced in males at comparable exposure levels. Otherwise, the compound did not cause adverse effects under conditions of this study. Food and water consumption and body weight gain were comparable in exposed and control groups. No treatment-related deaths were reported. Clinical chemistry and urinalysis did not differ significantly from controls. No gross or histopathological lesions were found.

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In a separate portion of this study, 5 male and 5 female rats were exposed to 0.5 ppm HCCPD vapor for 5 days (6 hours/day) and allowed to recover for up to 21 days. Another 10 rats of each sex were exposed to this same concentration for up to 2 weeks (6 hours/day, 5 days/week) with no recovery period. All of the males and 2 females exposed for 2 weeks died. There was bronchial erosion of the epithelium, hyperplastic changes in the cuboidal and columnar cells of the epithelium, inflammatory cell infiltration, and fibroblastic proliferation in the lungs of the treated animals. After 7 days for males and 10 days for females, there were significant increases in packed cell volume, hemoglobin concentration and erythrocyte count which were hypothesized to be a compensatory response for impaired lung function.

Three males from the recovery group died with 7 days of their fifth and last exposure, but all the females and two males survived. The histopathologic changes in the lung of the recovery group survivors were resolved when the animals were examined after sacrifice at the end of the recovery period.

Rand et al. (1982a) also studied the effects of inhalation exposure to HCCPD on monkeys. Groups of cynomolgous monkeys (6/sex/dose) were exposed to vapors of HCCPD at concentrations of 0, 0.01, 0.05, or 0.2 ppm for 13 weeks. Following exposure, clinical signs, and food and water consumption were monitored daily and body weights were recorded weekly during the treatment period. Blood chemistry, hematological and urinalysis parameters were evaluated. Gross necropsy was performed and organ weights (adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thyroid, and uterus) were determined. Histopathological examination was performed on the following organs or tissues after 13 weeks in the control and high-dose groups: adrenals, aorta, brain, eye, heart, esophagus, stomach, intestine, kidneys, larynx, liver, lungs, nasal turbinates, ovaries, lymph nodes, spleen, urinary bladder, pancreas, pituitary, prostate, uterus, seminal vesicles, skeletal muscle, trachea, testes, thymus, thyroid, parathyroid, sciatic nerve and salivary gland. No mortalities or adverse clinical signs were reported. Body weight and food consumption were comparable in exposed and control groups. No treatment-related effects on tissue weight were reported and the compound did not cause any gross or histopathological lesions in any tissues examined. Pulmonary function tests (e.g., lung mechanics, pulmonary ventilation, and blood gas analysis) were comparable in exposed and control groups. Erythrocyte sedimentation rate, packed cell volume, hemoglobin, red blood cell count, reticulocyte count, mean corpuscular hemoglobin concentration, mean cell volume, total white blood cell count, differential count and clotting time were comparable in exposed and control groups. Blood chemistry parameters (serum urea, total protein, albumin, cholesterol, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase) were comparable in exposed and control groups. Urine parameters (volume, pH, specific gravity, protein, reducing substances, glucose, ketones, bile pigments, urobilinogen and hemoglobin) were comparable in exposed and control groups.

In a separate experiment, groups of cynomologous monkeys were exposed to HCCPD vapors for up to 14 weeks. Animals (3M, 3F) from each treatment group were evaluated to determine the effects of the compound on the lungs, especially ultrastructural changes in Clara cells of the terminal bronchioles of the lungs. Except in one monkey, the compound did not cause histopathological lesions in the terminal bronchioles under the conditions of this study. Inclusions in the Clara cells were noted in one monkey. Since the Clara cells of the terminal bronchioles contain detoxifying enzymes and function to eliminate inhaled toxicants, the appearance of inclusion bodies is considered to be an indication of exposure, and not a sign of toxicity.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

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MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Hexachlorocyclopentadiene
CAS number(s): 77-47-4
Date: January 15, 1999
Profile status: Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 71
Species:rat

MRL: 0.0002 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: NTP. 1994. National Toxicology Program. Toxicology and carcinogenesis studies of hexachlorocyclopentadiene (CAS No. 74-47-4) in F344 rats and B6C3F1 mice. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP TR 437. NIH Publication No. 93-3168.

Experimental design: Groups of 50 male and 50 female rats were exposed to concentrations of 0, 0.01, 0.05, or 0.2 ppm HCCPD for 6 hours/day, 5 days/week for 2 years. At sacrifice, the tissues were examined for the occurrence of tumors and histological abnormalities.

Effects noted in study and corresponding doses: Yellow-brown pigmentation of the nose, trachea, and/or lungs was noted at sacrifice. At the lowest dose tested, 68% of the exposed females had pigmentation in the nasal epithelium; 0%, in the trachea; and 50% in the bronchioles. In males, 92% had pigmentation in the nasal epithelium; 0%, in the trachea; and 0% in the bronchioles. Although the number of affected animals and the severity of the pigmentation increased with dose, there was no clear dose-response trend. The occurrence of pigmentation apparently had little effect on survival based on a comparison of the Kaplan-Meier survival curves for the exposed and control animals. Chemical evaluation of the pigment indicated that it was a reducing substance and may have been either a ceroid or lipofuscin deposit. The 0.01 ppm dose was identified as the LOAEL in this study.

Dose endpoint used for MRL derivation: The 0.01 ppm LOAEL was selected as the basis for the MRL derivation. Exposure to this concentration of HCCPD for 6 hours/day, 5 days/week for 2 years resulted in the formation of yellow-brown pigment in the nasal, tracheal, and/or bronchial epithelium.

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [X] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [X] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

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

The chronic inhalation MRL for HCCPD is derived as follows.

$VE_A = (0.3\ m^3/d)^a \times (1000\ L/m^3) \times (1d/24\ hr) \times (1\ hr/60\ min) \times (1000\ mL/L) = 170\ mL/min$

$RGDR_{[PU]}{}^b = (VE/SA_{PU})_A/(VE/SA_{PU})_H = (210\ mL/min/0.34\ m^3)/(13800\ mL/min/54\ m^3) = 2.4$

$LOAEL_{HEC} = LOAEL \times RGDR = 0.01\ ppm \times 2.4 = 0.02\ ppm$

$MRL = LOAEL_{HEC} \div UF$

$MRL = 0.02\ ppm \div 90$

$MRL = 0.0002\ ppm$

[a]Average inhalation rate for male and female F344 rats for chronic duration.
[b]Derived from equation 4-28 of EPA 1994 (EPA/600/8-90-066F).

Was a conversion used from intermittent to continuous exposure? No. A conversion factor was not used to adjust for intermittent exposure due to the corrosive nature of HCCPD. The chemical exerts a direct contact effect, and the effects are concentration- rather than time-dependent.

Other additional studies or pertinent information that lend support to this MRL: NTP. 1994. National Toxicology Program. Toxicology and carcinogenesis studies of hexachlorocyclopentadiene (CAS No. 74-47-4) in F344 rats and B6C3F1 mice. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP TR 437. NIH Publication No. 93-3168.

Groups of 50 male and 50 female mice were exposed to concentrations of 0, 0.01, 0.05, or 0.2 ppm HCCPD for 6 hours/day, 5 days/week for 2 years. At sacrifice, the tissues were examined for the occurrence of tumors and histological abnormalities.

Yellow-brown pigmentation of the epithelium of the nose, trachea, and/or lungs was noted at sacrifice. At the lowest dose tested, 90% of the exposed males had pigmentation in the nasal epithelium; 58% had pigmentation in the trachea; and 4% had pigmentation in the lungs. In females, 80% had pigmentation in the nasal epithelium; 12% had pigmentation in the trachea; and 0% had pigmentation in the lings. Although the number of affected animals and the severity of the pigmentation increased with dose, there was no clear dose-response trend.

In a separate component of the NTP (1994) bioassay, groups of male mice were exposed to concentrations of 0.2 ppm HCCPD for 33 or 66 weeks, or to 0.5 ppm for 26 or 42 weeks under parallel exposure conditions (6 hours/day, 5 days/week). The animals were sacrificed at either 104 or 105 weeks and the respiratory tract tissue was examined. Pigmentation was found in the mucosa of the nose, trachea, and lungs of nearly all animals. Any pigmentation that formed in these tissues during exposure was still present 38 to 79 weeks after exposure ceased. The pigment apparently had little effect on survival because there were minimal differences among groups for the percent probability of survival or the number of animals surviving until study termination.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

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MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Hexachlorocyclopentadiene
CAS number(s): 77-47-4
Date: January 15, 1999
Profile status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 17
Species: rat

MRL: 0.1 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Abdo K, Montgomery CA, Kluwe WM, et al. 1984. Toxicity of hexachlorocyclopentadiene: subchronic (13-week) administration by gavage to F344 rats and B6C3F1 mice. J Appl Toxicol 4(2):75-81.

Experimental design: Groups of F344 rats (10/sex/dose) were administered HCCPD (0, 10, 19, 38, 75, 150 mg/kg/day) in corn oil by gavage, 5 days/week for 13 weeks. Body weights were determined initially and weekly during the treatment period. Clinical signs and mortality were monitored daily. Gross necropsy was performed and organ weights (liver, right kidney, thymus, heart, brain, and lungs) were determined. Histopathological examination was performed on the following organs or tissues after 13 weeks in the control, 75, and 150 mg/kg/day dose groups: skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib) thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach (also at 38, 19, and 10 mg/kg/day), duodenum, jejunum, ileum, colon, mesenteric nodes, liver, pancreas, spleen, kidney (also at 38, 19, and 10 mg/kg/day), adrenal, urinary bladder, seminal vesicle, prostate, testes, ovaries, uterus, nasal cavity, brain, pituitary, and spinal cord.

Effects noted in study and corresponding doses: Nephrosis was evident in both sexes at dose levels of 38 mg/kg/day or greater and effects were confined to the terminal portion of the proximal convoluted tubules in the inner cortex. The lower NOAEL of 10 mg/kg/day for the absence of forestomach lesions was not used as the basis of the MRL because humans do not possess a forestomach. Kidney weights were not affected. Because the batch of HCCPD used in the study also contained hexachlorobutadiene (0.5%) as and impurity, there may be some synergistic effect between the two chemicals at the highest doses. Forestomach hyperplasia was reported in females at dose levels of 19 mg/kg/day or greater. This effect was also seen in male rats, but occurred at doses of 38 mg/kg/day or greater. Focal inflammation of the forestomach was also observed in females (19 mg) and males (38 mg). Although the number of animals with inflammation increased in the exposed group compared to controls, it should be noted that the incidence of this lesion shoed a weak dose-related trend among the treatment groups. Ulcerations were detected in males in the 38 and 75 mg/kg/day dose groups, but were not reported in the high-dose group or in controls. No ulcerations were seen in female rats. Ruffled fur and inactivity occurred at dose levels of 75 mg, otherwise clinical signs were comparable in exposed and control groups. body weight was reduced a dose levels of 38 mg.

Dose endpoint used for MRL derivation: A NOAEL of 19 mg/kg/day was used to derive the MRL, based on the absence of effects on the kidneys. This dose was converted to 13.6 mg/kg/day, incorporating adjustments for intermittent exposure (5 days/week).

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

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

Was a conversion used from intermittent to continuous exposure?
If so, explain: 0.19 mg/kg/day x 5/7 = 0.1357 mg/kg/day

Other additional studies or pertinent information that lend support to this MRL: Abdo K, Montgomery CA, Kluwe WM, et al. 1984. Toxicity of hexachlorocyclopentadiene: subchronic (13-week) administration by gavage to F344 rats and B6C3F1 mice. J Appl Toxicol 4(2):75-81.

Groups of B6C3F1 mice (10/sex/dose) were administered HCCPD (0, 19, 38, 75, 150 mg/kg/day) in corn oil by gavage. Body weights were determined initially and weekly during the treatment period. Clinical signs and mortality were monitored daily. Gross necropsy was performed and organ weights (liver, right kidney, thymus, heart, brain, and lungs) were determined. Histopathological examination was performed on the following organs or tissues after 13 weeks in the control, 150, and 300 mg/kg/day dose groups: skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib) thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach (also at 38, 19, and 10 mg/kg/day), duodenum, jejunum, ileum, colon, mesenteric nodes, liver, pancreas, spleen, kidney (also at 38, 19, and 10 mg/kg/day), adrenal, urinary bladder, seminal vesicle, prostate, testes, ovaries, uterus, nasal cavity, brain, pituitary, and spinal cord.

Hyperplasia and inflammation of the forestomach were reported in both females (2/9, 22%) and males (2/10, 20%) at 38 mg/kg/day and also occurred at dose levels of 75 mg when compared to untreated controls. Although the number of animals showing forestomach lesions in he treated group was increased over untreated control levels, the incidence among all exposed groups showed a weak dose-related trend. Ulcerations were not observed in the control or exposed group (except at the high-dose in both sexes). There were also treatment-related lesions of the kidneys. Toxic nephrosis was observed in female mice at dose levels of 75 mg; kidney weights were not affected. Histopathological lesions were not seen in other organs, nor were there changes in organ weights. Clinical signs were comparable in exposed and control mice, except that ruffled fur and slight inactivity occurred at dose levels of 150 mg. Body weights were reduced at dose levels of 150 mg. Forestomach lesions appear to be the most sensitive end point under conditions of this study. A NOAEL of 19 mg/kg/day is identified for this study based on this end point.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX B
USER'S GUIDE

Chapter 1
Public Health Statement

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

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

Chapter 2
Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-l and 2-2) 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).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-l and Figure 2-l 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 2-l

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 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-l) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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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 2-l).

5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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 Frequencv/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 1 S), 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, dermal, and 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.

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 endpoint 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 8 of the profile.

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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 2-1

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, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

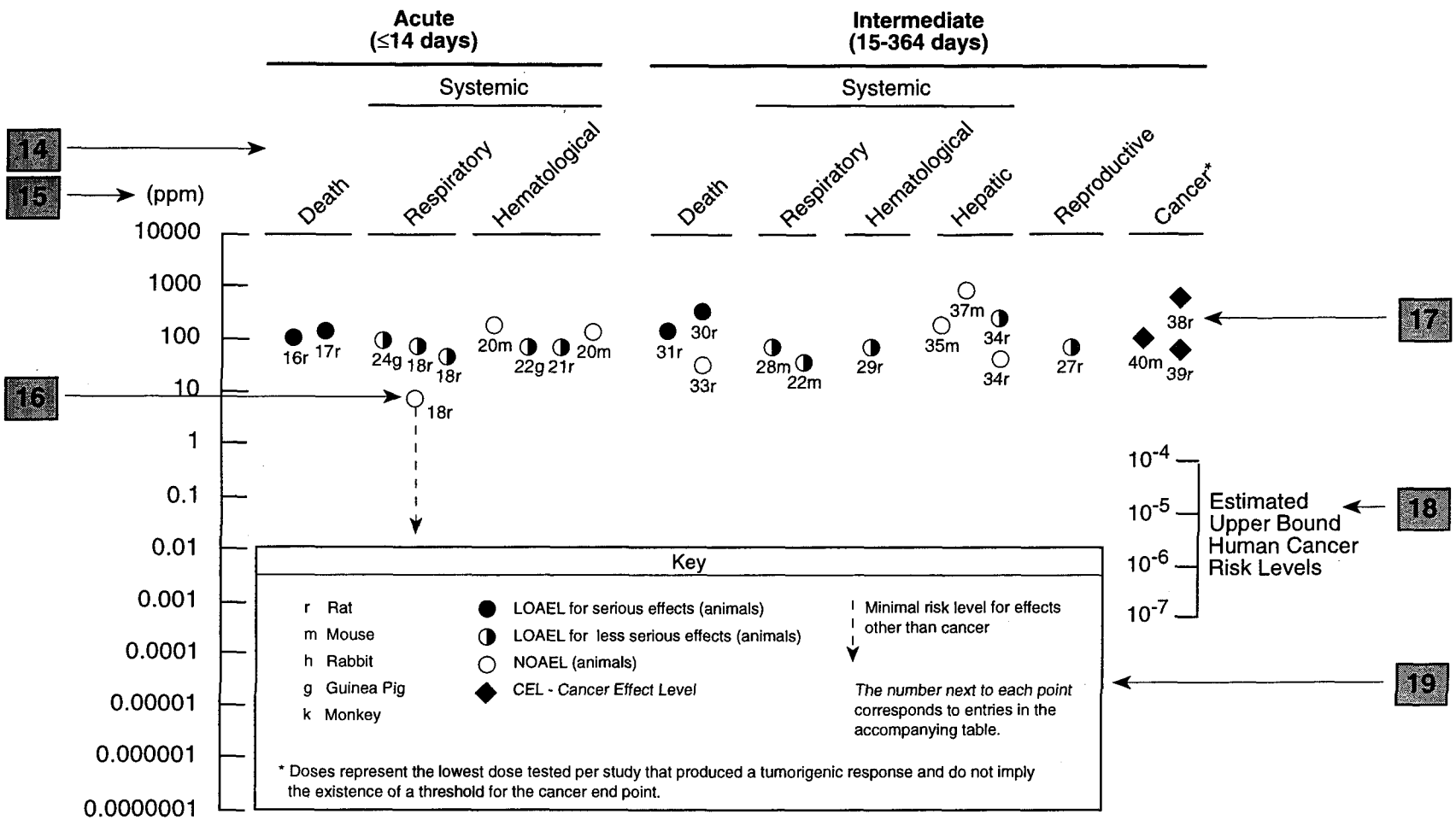
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE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

[a] The number corresponds to entries in Figure 2-1.

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10 ppm^3; 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

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section 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 section. 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 Data Needs section.

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 2.5, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.8, “Interactions with Other Substances,” and 2.9, “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).

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To derive an MRL, ATSDR generally selects the most sensitive endpoint 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 endpoint 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.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
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
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter

mm Hg	millimeters of mercury
mmol	millimole
mo	month
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
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
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
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
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
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
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard 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 Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	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

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