APPENDIX A

ATSDR MINIMAL RISK LEVEL

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 (l-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 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.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEETS

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ]Intermediate [ ] Chronic
Key to figure: 22
Species: Mouse
MRL: 0.1 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Larson JL, Wolf DC, Morgan KT, et al. 1994c. The toxicity of 1-week exposures to inhaled chloroform in female $B6C3F_1$ mice and male F-344 rats. Fund Appl Toxicol 22:431-446.

Experimental design: The authors investigated the ability of chloroform vapors to produce toxicity and regenerative cell proliferation in female $B6C3F_1$ mice and male Fischer 344 rats. Groups of 5 animals were exposed to 0, 1, 3, 10, 30, 100, or 300 ppm chloroform via inhalation for 6 hours a day for 7 consecutive days. Actual exposure concentrations measured for mice were 0, 1.2, 3.0, 10.0, 29.5, 101, and 288 ppm and for rats were 0, 1.5, 3.1, 10.4, 29.3, 100, and 271 ppm. Necropsies were performed on day 8. Animals were administered bromodeoxyuridine (BrdU) via implanted osmotic pump for the last 3.5 days. Cell proliferation was quantitated as the percentage of cells in S-phase (labeling index = LI) measured by the immunohistochemical detection of BrdU-labeled nuclei.

Effects noted in study and corresponding doses:

Female Mice:

300 ppm: Respiratory NOAEL; proximal tubules of kidney lined by regenerating epithelium (less serious LOAEL).

100 ppm: Renal NOAEL; centrilobular hepatocyte necrosis and severe diffuse vacuolar degeneration of midzonal and periportal hepatocytes (serious LOAEL); weight loss (less serious LOAEL).

30 ppm: Body weight NOAEL

10 ppm: Mild-to-moderate vacuolar changes in centrilobular hepatocytes (less serious LOAEL).

3 ppm: Hepatic effects NOAEL

Male Rats:

300 ppm: Swelling and mild centrilobular vacuolation of hepatocytes (less serious LOAEL).

100 ppm: Hepatic effects NOAEL.

30 ppm: Increased number of S-phase nuclei for tubule cells in the renal cortex (less serious LOAEL).

10 ppm: Renal effect NOAEL; decreased body weight gain (less serious LOAEL); epithelial goblet cell hyperplasia and degeneration of Bowman's glands in olfactory mucosa (less serious LOAEL).

3 ppm: Body weight gain and respiratory NOAEL.

Dose and end point used for MRL derivation:
[X] NOAEL [ ] LOAEL: 3 ppm for hepatic effects in mice

Uncertainty factors used in MRL derivation: 30
[ ] 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: No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
For dosimetry adjustment, the human equivalent concentration (HEC) is calculated based on a NOAEL of 3 ppm using Equation 4-10 (EPA 1990b). This equation was used due to the observation that chloroform achieves "periodicity" within 10% of the exposure duration (see Table A-1 below). Using Equation 4-10, the calculation is:

$$NOAEL_{(HEC)} = NOAEL \times [(blood{:}air\ coeff)_{mouse}/(blood{:}air\ coeff)_{human}]$$

given that the ratio of the blood:air partition coefficients are <1. In the case of chloroform, using the blood:air partition coefficients for the mouse is 21.3 and for the human is 7.34 (Corley et al. 1990), the ratio of mouse:human partition coefficients (21.3/7.34) is >1, therefore a default value of 1 is used to derive the $NOAEL_{HEC}$:

$$NOAEL_{HEC} = 3\ ppm \times 1$$
$$NOAEL_{HEC} = 3\ ppm$$

where:

$NOAEL_{[HEC]}$ = Human Equivalent Concentration of the NOAEL (no-observed-adverse effect level)

The MRL calculation is as follows:

$$MRL = NOAEL_{[HEC]} / UF$$
$$MRL = 3\ ppm / 30$$
$$MRL = 0.1\ ppm$$

Was a conversion used from intermittent to continuous exposure?
If so, explain: No.

Other additional studies or pertinent information that lend support to this MRL:
The Larson et al. (1994c) study is accompanied by a companion study performed by Mery et al. (1994), which examined the nasal lesions much more closely than this Larson study. The purpose of the Mery et al. study was to determine nasal cavity site-specific lesions and any cell induction/ proliferation associated with varying concentrations of chloroform (0, 1, 3, 10, 30, 100, 300 ppm) inhaled by both rats and mice 6 hours a day for 7 days. Female $B6C3F^1$ mice and male Fischer 344 rats were used. Tissue abnormalities seen grossly, histopathologically, enzymatically (cytochrome P-450 levels), and in cell proliferation (BrdU labeling of cells in the S-phase) were reported for both rats and mice. The respiratory epithelium of the nasopharyngeal meatus exhibited an increase in the size of goblet cells at 100 and 300 ppm chloroform, in addition to an increase in both neutral and

acidic mucopolysaccharides. Affected epithelium was up to twice the normal thickness. New bone formation within the nasal region was prominently seen at 10 ppm and above and followed a concentration response curve. At 1 ppm, only 1 animal showed mild bone enlargement of the first endoturbinate, with no changes seen at 3 ppm. At 10 ppm, minor enlargement was present in all animals. At 30 and 100 ppm, new osseous spicules was present at the beginning of the first endoturbinate, while at 300 ppm, the width of the new bone was almost doubled compared to controls receiving no chloroform, with lesions extending to involve up to 75% of the turbinate in all of the sites studied. Enzymatically, staining for P-450-2E1 was most prominent in the control animals in the cytoplasm of olfactory epithelial sustentacular cells and in the acinar cells of Bowman's glands, and more intense in the superficial cells than in the deep cells. In general, starting at about 3 ppm, increasing the chloroform concentration tended to decrease the amount of P-450 staining. Exposure to chloroform resulted in a dramatic increase in the number of S-phase nuclei. A clear proportional concentration-related effect was observed, with the proliferative response confined to activated periosteal cells, including both osteogenic (round) and preosteogenic (spindle) cells. The proximal and central regions of the first endoturbinate had the highest increase of cell proliferation, while the distal part had only a moderate response, with this response being statistically significant from controls at concentrations of greater than 10 ppm. Decreased body weight was observed at 300 ppm only (data not provided). In mice, decreased body weight was observed at 100 and 300 ppm (data not provided). The only treatment-related histologic change observed in female mice was a slight indication of new bone growth in the proximal part of the first endoturbinate in one mouse exposed to 300 ppm chloroform. The S-phase response was observed at chloroform concentration of 10 ppm and higher.

Using the Corley PBPK model for chloroform (Corley et al. 1990) in the Scop version (courtesy of Dr. Nancy Chiu, USEPA) to simulate the mouse exposure of chloroform by inhalation. This data is presented below:

Table A-1. Corley PBPK Model for Chloroform to Simulate Mouse Exposure by Inhalation

Time (hrs):	Blood Concentration (CA) (mg/L):
0.00	0.014
0.25	0.040
0.50	0.041
0.75	0.041
1.25	0.042
1.50	0.042
1.75	0.042
2.00	0.042
2.25	0.042
2.50	0.042
3.375	0.042
4.5	0.042
5.625	0.042
6.75	0.0006

Source: Corley et al. (1990) in the Scop version (courtesy of Dr. Nancy Chiu, USEPA).

The data furnished by this model demonstrates that the arterial blood concentration (CA) of chloroform in the mouse exposed to 3 ppm of chloroform for 6 hours reached "periodicity" within 15 minutes following exposure. This data allowed the use of EPA (1990b) Equation 4-10 to derive the acute-duration inhalation MRL for chloroform exposure.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 39
Species: Human

MRL: 0.05 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Phoon WH, Goh KT, Lee LT, et al. 1983. Toxic jaundice from occupational exposure to chloroform. Med J Malaysia 38:31-34.

Experimental design: The study describes outbreaks of toxic hepatitis in workers occupationally exposed to chloroform in two different factories. Mostly women were employed in both places.

Effects noted in study and corresponding doses: The workers in the first outbreak were exposed to concentrations up to 400 ppm chloroform in the workplace. No other chemical was involved. Blood chloroform levels in exposed workers ranged from 0.10 to 0.29 mg/100 mL. Workplace concentration levels of chloroform ranged from 14 to 50 ppm in the second outbreak. Vomiting and toxic hepatitis were noted to occur at an inhaled concentration of 14 ppm (less serious LOAEL). All affected workers were exposed to chloroform for less than six months. The patients exhibited anorexia, nausea, vomiting, and jaundice without fever. The subjects had originally been diagnosed with viral hepatitis, however the diagnosis of toxic hepatitis due to chloroform exposure was based upon epidemiological considerations.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL : 14 ppm for hepatic effects

Uncertainty factors (UF) used in MRL derivation: 100

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Modifying factor (MF) used in MRL derivation:

[ ] 1 [X] 3 [ ] 10 (for insufficient diagnostic data to determine the seriousness of hepatotoxic effects)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: No.

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

No factors were used to convert to a human equivalent dose, since the data obtained from this study was obtained from human exposures to chloroform.

The MRL calculation is as follows:

MRL = LOAEL / (UF x MF)

MRL = 14 ppm / (100 x 3)

MRL = 0.05 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: No.

Other additional studies or pertinent information that lend support to this MRL:

The study by Bomski et al. (1967) noted similar finding in a group of 68 workers occupationally exposed to chloroform for 1–4 years in a pharmaceutical plant. Inhaled chloroform concentrations ranged from 0.01 to 1 mg/L. Other solvents were reported in the air in trace amounts. Hepatomegaly was found in 25% of chloroform-exposed workers. Toxic hepatitis was found in 5.6% of the liver enlargement cases. The workers were diagnosed as having hepatosplenomegaly, enhanced serum glutamic pyruvic transaminase [SGPT] and serum glutamic oxaloacetic transaminase [SGOT] activities, and hyper-gammaglobulinemia. Hepatosteatosis (fatty liver) was detected in 20.6% of liver-enlargement cases. Chloroform-exposed workers had a higher frequency of jaundice over the years than the control group.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ]Intermediate [X] Chronic
Key to figure: 51
Species: Human

MRL: 0.02 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Bomski H, Sobolewska A, Strakowski A. 1967. [Toxic damage of the liver by chloroform in chemical industry workers.] Int Arch F Gewerbepathologie u. Gewerbehygiene 24:127-134 (German).

Experimental design: A group of 68 workers occupationally exposed to chloroform for 1–4 years in a pharmaceutical plant were examined. Doses of inhaled chloroform ranged from 2 to 205 ppm over a 1–4-year-period. Air concentrations of chloroform ranged from 0.01 mg/L to 1 mg/L. Other solvents were reported in the air in trace amounts.

Effects noted in study and corresponding doses: A systemic LOAEL (hepatomegaly) of 2 ppm was determined from the data presented in this study. Hepatomegaly was found in 25% of chloroform exposed workers. The results were compared with a group of unexposed controls, and a group of persons who had infectious hepatitis during the last 1–4 years. Toxic hepatitis was found in 5.6% of the liver enlargement cases (the workers were diagnosed as having hepatosplenomegaly, enhanced SGPT and SGOT activities, and hyper-gammaglobulinemia). Hepatosteatosis (fatty liver) was detected in 20.6% of liver-enlargement cases. Functional tests were negative in most of the subjects; a biopsy was not performed in any case. Chloroform-exposed workers had a higher frequency of jaundice over the years than the control group. The authors speculated that a viral infection might have been promoted in the chloroform damaged liver.

Dose end point used for MRL derivation:

[ ] NOAEL [X] LOAEL: 2 ppm for hepatic effects

Uncertainty factors used in MRL derivation: 100

[ ] 1 [ ] 3 [X] 10 (for use of a LOAEL)
[ ] 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: No.

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

No factors were used to convert to a human equivalent dose, since the data obtained from this study was obtained from human exposures to chloroform.

The MRL calculation is as follows:

MRL = LOAEL / (UF)

MRL = 2 ppm / (100)

MRL = 0.02 ppm

Was a conversion used from intermittent to continuous exposure?
If so, explain: No.

Other additional studies or pertinent information that lend support to this MRL:

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ]Intermediate [ ] Chronic
Key to figure: 28
Species: Mouse

MRL: 0.3 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Larson JL, Wolf DC, Butterworth BE. 1994b. Induced cytotoxicity and cell proliferation in the hepatocarcinogenicity of chloroform in female $B6C3F_1$ mice: comparison of administration by gavage in corn oil vs ad libitum in drinking water. Fund Appl Toxicol 22:90-102.

Experimental design:

This study was designed to identify a relationship between the magnitude and duration of chloroform-induced histopathologic and proliferative responses for female mice dosed with chloroform in the drinking water vs those dosed in corn oil via gavage. Authors placed 0, 60, 200, 400, 900, or 1,800 ppm of chloroform in drinking water; however, due to decreased water intake, the authors' calculation of consumed chloroform was 0, 16, 26, 53, 81, or 105 mg/kg/day.

Effects noted in study and corresponding doses:

In the 400, 900, and 1,800 ppm treatment groups, the livers had tinctorial changes characterized by pale cytoplasmic eosinophilic staining of centrilobular hepatocytes compared to the periportal hepatocytes and controls. Livers from mice treated with 200 ppm (26 mg/kg/day actual intake) chloroform or less failed to showed significant histologic changes when compared to controls. Thus the dose of 26 mg/kg/day was considered the NOAEL for hepatic effects in these mice. Chloroform exposure did cause a slight dose dependent decrease in number of cells in S-phase in the kidneys, mainly in the cortex, while there was an increase in these type of cells in the outer medullary region. Decreased body weight was observed at the two highest doses. After 4 days treatment, serum clinical chemistry analyses were not different from controls in either liver alanine aminotransferase (ALT) or sorbitol dehydrogenase (SDH) at any dose.

Dose end point used for MRL derivation:

[X] NOAEL [ ] LOAEL: 26 mg/kg/day for hepatic effects in mice

Uncertainty factors used in MRL derivation: 100

[ ] 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:

Conversion of the ppm concentration of chloroform in the drinking water to a mg/kg/day dose was provided by the authors of the paper.

The MRL calculation is as follows:

MRL = NOAEL / UF

MRL = 26 mg/kg/day / 100

MRL = 0.3 mg/kg/day

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

Was a conversion used from intermittent to continuous exposure?
If so, explain:

Other additional studies or pertinent information that lend support to this MRL:

Larson et al. (1995) also studied the dose response relationships for the induction of cytolethality and regenerative cell proliferation in male Fischer 344 rats given chloroform in corn oil by gavage or in the drinking water. Groups of 12 rats were administered oral doses of 0, 3, 10, 34, 90, and 180 mg/kg/day chloroform in corn oil by gavage for 4 or for 5 days a week for 3 weeks. BrdU was administered via an implanted osmotic pump to label cells in S-phase. Statistically significant decreases in body weight gains were observed in the 180 mg/kg/day dose group at 4 days and in the 90 and 180 mg/kg/day dose groups at 3 weeks. At 34 mg/kg/day, slight-to-mild centrilobular sinusoidal leukostasis was observed after 4 days of exposure. The livers of rats given 90 mg/kg/day for 4 days had a slight increase in centrilobular pallor and necrosis of hepatocytes surrounding the central vein; the remaining central and some mid-zonal hepatocytes were swollen and displayed a cytoplasmic granularity. After 3 weeks of exposure, livers of rats in the 34 or 90 mg/kg/day dose groups did not differ from controls. In the 180 mg/kg/day dose group, the livers of rats after 4 days had scattered individual cell necrosis throughout the central and midzonal regions. The cytoplasm of the centrilobular hepatocytes was pale eosinophilic and mildly vacuolated. In the 180 mg/kg/day dose group, after 3 weeks effects were similar to those seen at 4 days after exposure. Dose-dependent increases in both ALT and SDH were observed at 4 days in the 90 and 180 mg/kg/day dose groups and at 3 weeks in the 180 mg/kg/day dose group only. A dose-dependent increase in LI was seen in rat liver after 4 days of treatment with 90 and 180 mg/kg/day by gavage, but the LI remained elevated after 3 weeks of treatment only at the 180 mg/kg/day dose. At doses of 0, 60, 200, 400, 900, and 1,800 ppm for 4 days, no microscopic alterations were seen in the kidneys after 4 days of treatment. As a general observation, rats treated for 3 weeks with 200 ppm chloroform and greater had slightly increased numbers of focal areas of regenerating renal proximal tubular epithelium and cell proliferation than were

noted in controls, but no clear dose response relationship was evident. However, the overall renal LI was not increased at any dose or time point. Similarly, only mild hepatocyte vacuolation was observed in rats given 900 or 1,800 ppm in water for 4 days and in rats given 1,800 ppm in water for 3 weeks. No increase in the hepatic LI was observed at any time point. When chloroform was administered in the drinking water at doses of 0, 60, 200, 400, 900, and 1,800 ppm for 3 weeks, no microscopic alterations were seen in the kidneys after 4 days of treatment. As a general observation, rats treated for 3 weeks with 200 ppm chloroform and greater had slightly increased numbers of focal areas of regenerating renal proximal tubular epithelium and cell proliferation than were noted in controls, but no clear dose response relationship was evident. However, the overall renal LI was not increased at any dose or time point. Similarly, only mild hepatocyte vacuolation was observed in rats given 900 or 1,800 ppm in water for 4 days and in rats given 1,800 ppm in water for 3 weeks. No increase in the hepatic LI was observed at any time point. The authors noted that these data indicated more severe hepatic and renal toxicity when chloroform is administered by gavage than in the drinking water.

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 68
Species: Dog

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

Reference: Heywood R, Sortwell RJ, Noel PRB, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J Environ Pathol Toxicol 2:835-851.

Experimental design: An intermediate oral exposure MRL of 0.1 mg/kg/day was derived using the study by Heywood et al. (1979). The study was 7.5 years in duration in which 8 male and 8 female Beagle dogs were exposed to chloroform in toothpaste capsules, with doses of 0, 15, and 30 mg/kg/day, 6 days a week for 6 weeks. Clinical chemistry parameters were monitored at 6 and 13 weeks of exposure and thereafter at intervals of 8–32 weeks.

Effects noted in study and corresponding doses: Serum glutamic pyruvic transaminase (SGPT) activity was significantly increased ($p<0.05$) in the 30 mg/kg/day group beginning at 6 weeks and at every interval thereafter. SGPT activity was not increased in the 15 mg/kg/day group until week 130. Thus, 15 mg/kg/day is the NOAEL for intermediate duration exposure.

Dose end point used for MRL derivation:

[X] NOAEL [ ] LOAEL : 15 mg/kg/day for hepatic effects

Uncertainty factors used in MRL derivation: 100

[ ] 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:

No.

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

Was a conversion used from intermittent to continuous exposure?
If so, explain:

(15 mg/kg/day) x 6/7 days = 12.9 mg/kg/day

The MRL calculation is as follows:

$$MRL = NOAEL_{[ADJ]} / UF$$

$$MRL = 12.9 \text{ mg/kg/day} / 100$$

$$MRL = 0.1 \text{ mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL:

Liver effects in animals have been reported in numerous oral studies of intermediate duration. Fatty changes, necrosis, increased liver weight, and hyperplasia have been observed in rats exposed to ≥150 mg/kg/day chloroform in drinking water for 90 days (Palmer et al. 1979). An increased incidence of sporadic, mild, reversible liver changes occurred in mice exposed to chloroform in drinking water at doses of 0.3–114 mg/kg/day for 90 days, but the incidences were not significantly higher than the incidences in controls (Chu et al. 1982a). Fatty and hydropic changes, necrosis, and cirrhosis were observed in mice treated by gavage with ≥50 mg/kg/day chloroform in oil for 90 days (Bull et al. 1986; Munson et al. 1982) or at 86 mg/kg/day in drinking water for 1 year (Klaunig et al. 1986). In contrast, centrilobular fatty changes observed in mice at 64 mg/kg/day chloroform in drinking water for 90 days appeared to be reversible (Jorgenson and Rushbrook 1980), and no liver effects were found in mice treated with ≥50 mg/kg/day in aqueous vehicles (Bull et al. 1986). In addition, hepatocellular degeneration was induced in F_1 females in a 2-generation study in which mice were treated by gavage with 41 mg/kg/day chloroform in oil (Gulati et al. 1988).

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Chloroform
CAS number(s): 000067-66-3
Date: March 19, 1997
Profile status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ]Intermediate [X] Chronic
Key to figure: 89
Species: Dog

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

Reference: Heywood R, Sortwell RJ, Noel PRB, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. J Environ Pathol Toxicol 2:835-851.

Experimental design: Eight male and 8 female Beagle dogs were exposed to chloroform in toothpaste capsules. Doses used were 0, 15, and 30 mg/kg/day, 6 days a week for 7.5 years. Clinical chemistry parameters were monitored at 6 and 13 weeks of exposure and thereafter at intervals of 8–32 weeks for 7.5 years.

Effects noted in study and corresponding doses: SGPT activity was significantly increased ($p<0.05$) in the 30 mg/kg/day group beginning at 6 weeks and at every interval thereafter. SGPT activity was not increased in the 15 mg/kg/day group until week 130. No treatment-related body weight changes were observed in chloroform exposed dogs. No hematological changes were found. Increased SGPT levels, and less distinct elevation of SGOT and SAP seemed to be dose-related. However, the SGPT levels tended to return to normal during the recovery period. Bromsulphalein retention test was performed during the sixth year of the study; no treatment-related abnormality was found. No organ weight changes were found in the exposed groups. No remarkable histopathological differences were observed in dogs regarding the cardiovascular system. Fatty cysts were observed in the liver in all groups; however, in females the incidence seemed to be dose-related (3 of 12, 5 of 8, 7 of 8). Fat deposition in renal glomeruli was reportedly higher in the 30 mg/kg/day chloroform group.

Dose end point used for MRL derivation:

[ ] NOAEL [X] LOAEL: 15 mg/kg/day for hepatic effects

Uncertainty factors used in MRL derivation: 1000

[ ] 1 [ ] 3 [X] 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: No.

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

Was a conversion used from intermittent to continuous exposure?
If so, explain:

(15 mg/kg/day) x 6/7 days = 12.9 mg/kg/day.

The MRL calculation is as follows:

$$MRL = LOAEL_{[ADJ]} / UF$$

$$MRL = 12.9 \text{ mg/kg/day} / 1000$$

$$MRL = 0.01 \text{ mg/kg/day}$$

Other additional studies or pertinent information that lend support to this MRL:

Numerous chronic-duration oral studies examined hepatic and renal end points as well as neurological and cancer effects. Serious effects occurred at higher doses; 15 mg/kg/day was the lowest dose used in available animals studies. A NOAEL of 2.46 mg/kg/day for liver and kidney effects (SGPT, SGOT, BUN and SAP) was found in humans who used a dentifrice containing 0.34% or a mouthwash containing 0.43% chloroform for 1–5 years (DeSalva et al. 1974).

Agency Contact (Chemical Manager): Selene Chou

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- 1 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 endpoints, 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- 1) 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.

(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 2.4, "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 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 toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(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 0.0005 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.

(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.

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(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 0.0005 ppm.

LEGEND

See Figure 2-l

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

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 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 inhalationexposure 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 0.0005 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**

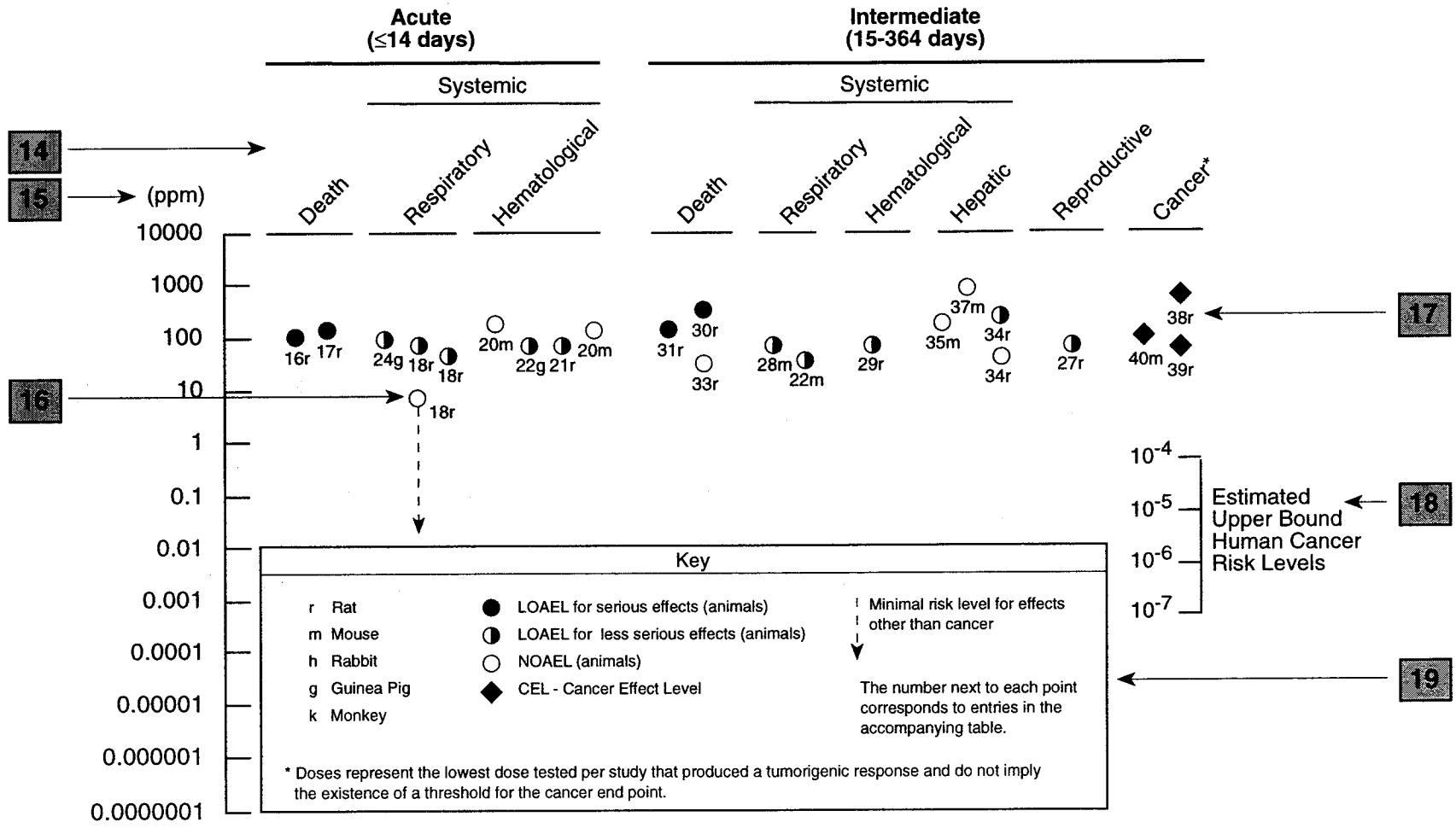
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC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

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



APPENDIX B

Chapter 2 (Section 2.4)

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 endpoints 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 endpoints 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 endpoints (if derived) and the endpoints 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 2.4, “Relevance to Public Health,” contains basic information known about the substance. Other sections such as 2.6, “Interactions with Other Substances,” and 2.7, “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 advers 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 (UT) 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
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
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
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
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
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
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
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio

STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
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
δ	delta
γ	gamma
μm	micrometer
μg	microgram

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