APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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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 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 2,3-Dichloropropene
CAS Numbers: 78-88-6
Date: June 2008
Profile Status: Final Draft Post-public
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 3
Species: Rat

Minimal Risk Level: 0.002 [ ] mg/kg/day [X] ppm

Reference: Zempel JA, Grandjean M, Young JT. 1987. 2,3-Dichloropropene: Results of a two-week inhalation toxicity study in Fischer-344 rats and B6C3F1 mice. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section FYI. OTS0000499-1.

Note: The principal study is an unpublished study that has been peer reviewed.

Experimental design: Groups (five/sex/concentration) of B6C3F1 mice and F344 rats were exposed to vapors of 2,3-dichloropropene (>99% purity) 6 hours/day for nine exposures over 11 days at concentrations of 0, 5, 25, or 75 ppm (0, 22.7, 113.5, or 340 mg/m^3). Animals were examined daily for signs of toxicity. Body weights were measured on days 1, 3, 5, and 12. Urine samples were collected from rats before the last exposure on day 11. At termination on day 12 after an overnight fast, blood samples were taken from rats and mice for hematology and serum chemistry analyses. All rats and mice received a complete necropsy examination that, for rats, included the eyes. Absolute and relative organ weights were recorded and calculated for brain, heart, liver, thymus, kidneys, and testes. All saved tissues were examined microscopically for all animals in the control and 75 ppm groups; in the 5 and 25 ppm groups, target tissues were examined for histopathology (liver, kidneys, bone marrow, lungs, and nasal tissues in both species, and also thymus, trachea, and larynx in mice). The study was conducted under Good Laboratory Practice standards.

Effects noted in study and corresponding doses: NOAELs were not identified in rats or mice. The lowest tested concentration, 5 ppm, was a LOAEL for respiratory lesions in both species.

Rats: Treatment caused no significant changes in survival, daily activities, or hematology, serum chemistry, or urinalysis results in rats. Statistically significant reductions in body weight in ≥25 ppm groups compared to controls were not biologically significant. Observed organ weight changes reflected changes in body weight and were not accompanied by histopathology. Histopathology of the respiratory tract was the major effect of exposure, showing concentration-related increases in severity. In all rats exposed at 25–75 ppm, slight-to-moderate degeneration (thinning) of the nasal olfactory epithelium was observed, secondarily producing inflammation and sloughing of necrotic cells. Hyperplasia of the nasal respiratory epithelium was observed in nearly all treated rats except for one male treated at 5 ppm: the severity of this lesion was very slight at ≥5 ppm, slight at 25 ppm, and moderate at 75 ppm (Table A-1). Slight peribronchiolar infiltration of eosinophils was observed in one male at 5 ppm and most rats at 25–75 ppm, but the study authors were uncertain as to the toxicological significance of this lesion. In male and female rats, 5 ppm was a LOAEL for hyperplasia of the nasal respiratory epithelium.

Table A-1. Incidence of Significant Lesions in Fischer 344 Rats and B6C3F1 Mice Exposed to 2,3-Dichloropropene (>99%) Vapor 6 Hours/Day, for 9/11 Days[a]

	Control	5 ppm	25 ppm	75 ppm
Rats				
Hyperplasia of nasal respiratory epithelium				
Male	0/5	4/5*	5/5**	5/5***
Female	0/5	5/5*	5/5**	5/5***
Mice				
Hyperplasia of nasal respiratory epithelium				
Male	0/5	3/5*	5/5**	5/5***
Female	0/5	4/5*	5/5**	5/5***
Diffuse degeneration of bronchial/bronchiolar epithelium				
Male	0/5	5/5**	5/5***	5/5****
Female	0/5	5/5**	3/5***+ 2/5****	5/5****

[a]Severity: *very slight; **slight; ***moderate; ****severe

Source: Zempel et al. 1987

Mice: Treatment had no significant effect on survival in mice. Upon repeated exposure, reduced activity levels were observed in all groups in a concentration-related manner; beginning with the third exposure at 25 or 75 ppm, slow and labored respiration was observed during exposure on days 3 and 5. Food intake (as estimated by fecal output) appeared to be reduced in the 25 and 75 ppm groups during the first week. Body weights were significantly lower compared to controls by 12–25% in males and 16–26% in females exposed at 25 or 75 ppm. According to the study authors, hematology and serum chemistry changes indicated mild dehydration and stress-induced lymphopenia at ≥25 ppm rather than direct toxic effects of the compound (for example, increased ALT at 75 ppm was not accompanied by histology, but seemed to be a consequence of hemoconcentration). At gross necropsy, the size and weight of the thymus were reduced in male and female mice exposed at ≥25 ppm. Microscopic examination showed diffuse cortical atrophy of the thymus, which study authors considered secondary to stress, at 75 ppm. Histopathology of the respiratory tract was the most significant effect of exposure and showed concentration-related increases in severity (Table A-1). Slight-to-moderate degeneration of nasal olfactory epithelium was observed at ≥25 ppm and very slight-to moderate hyperplasia of the nasal respiratory mucosa occurred at ≥5 ppm. Hyperplasia (very slight-to-slight) of the laryngeal epithelium was observed at ≥25 ppm. In the bronchial/bronchiolar tissue, a diffuse degenerative lesion of the ciliated respiratory epithelium was slight at 5 ppm (irregular cells size and apical nuclei in many cells), moderate at 25 ppm and severe at 75 ppm, showing flattened or cuboidal epithelium (rather than columnar) with sparse ciliation and apical rather than basal nuclei. In male and female mice, 5 ppm was a LOAEL for very slight hyperplasia of the nasal respiratory epithelium and slight diffuse degeneration of the bronchial/bronchiolar epithelium.

Dose and end point used for MRL derivation: Very slight hyperplasia of nasal respiratory epithelium in female rats exposed to 5 ppm 2,3-dichloropropene (>99% purity), 6 hours/day, for 9/11 days. The effect is considered minimal because the severity of the lesion was characterized by the study authors as very slight. Using EPA (1994) dosimetric adjustments (see below), a regional gas dose ratio ($RGDR_{ET}$) of 0.1143 for extrathoracic effects was applied to the duration-adjusted LOAEL of 1.25 ppm, resulting in a human equivalent concentration ($LOAEL_{HEC}$) of. 0.1429 ppm, the point of departure for the MRL.

[ ] NOAEL [X] $[LOAEL]_{HEC}$

Uncertainty Factors used in MRL derivation: 90 applied to the $LOAEL_{HEC}$ of 0.1429 ppm

[X] 3 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans using dosimetric adjustments
[X] 10 for human variability

0.1429 ppm / 90 = 0.0016 ppm, rounded to 0.002 ppm

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: EPA (1994) methods for calculating dosimetric adjustments across species for inhalation exposures were applied to data for nasal lesions, defined as extrathoracic (ET) effects, in rats and mice, and for bronchial and bronchiolar lesions, defined as trachiobronchial (TB) effects, in mice. Values used in these calculations and the calculated regional gas dose ratios are given in Table A-2.

Table A-2. Values Used for Calculating Human Equivalent Concentrations to LOAELs of 5 ppm for Fischer F344 Rats and B6C3F1 Mice Exposed 6 Hours/Day, 9/11 Days to 2,3-Dichloropropene[a]

		Rats		Mice	
	Human	Male	Female	Male	Female
Intercept b_0[b]		-0.578	-0.578	0.326	0.326
Slope b_1[b]		0.821	0.821	1.050	1.050
Time-weighted-average body weight[c] (kg)		0.2326 kg	0.1502 kg	0.0254 kg	0.0211 kg
VE (minute volume) (mL/minute)	13,800[b]	169.42	118.3106	29.2857	24.1033
SA_{ET} (surface area of extra-thoracic region)[b]	200 cm^2	15 cm^2	15 cm^2	3 cm^2	3 cm^2
$RGDR_{ET}$		0.1637	**0.1143**	0.1415	0.1164
$(LOAEL\text{-}adjusted)_{HEC\text{-}ET}$ (ppm)		0.2046	**0.1429**	0.1769	0.1455
SA_{TB} (surface area of tracheo-bronchial region)[b]	3,200 cm^2	Not applicable	Not applicable	3.5 cm^2	3.5 cm^2
$RGDR_{TB}$		Not applicable	Not applicable	1.7771	1.4305
$(LOAEL\text{-}adjusted)_{HEC\text{-}TB}$ ppm		Not applicable	Not applicable	2.2214	1.7881

[a]Zempel et al. (1987)
[b]EPA (1994)
[c]Calculated from data in Zempel et al. (1987)

Although 2,3-dichloropropene is a category 2 gas, the extrathoracic (ET) regional gas dose ratios (RGDRs) were calculated from rat and mouse data using the equation for a category 1 gas by default, since an equation is not available for category 2 gases (EPA 1994).

$$RGDR_{ET} = (RGD_{ET})_{rodent} / (RGD_{ET})_{human} = (VE/SA_{ET})_{rodent} / (VE/SA_{ET})_{human}$$

The tracheobronchial (TB) regional gas dose ratios were calculated from mouse data using the equation for a category 1 gas by default.

$RGDR_{TB} = (RGD_{TB})_{mouse} / (RGD_{TB})_{human}$
$= [(VE/SA_{TB})_{mouse} / (VE/SA_{TB})_{human}] [(e^{-[SAet/VE]mouse}) / (e^{-[SAet/VE]human})]$

Where:
VE = minute volume in mL/minute
SA = surface area in cm^2

The minute volumes (VE) for male and female rats and mice were calculated using the equation $LN (VE) = b_0 + b_1 [LN (BW in kg)]$.

Slopes and intercepts for rats and mice were taken from EPA (1994). The acute time-weighted-average body weights for male and female B6C3F1 mice, and male and female Fischer 344 rats, were calculated from data reported in the key study. Values for calculating minute volumes are in Table A-2.

The calculated regional gas dose ratios for extrathoracic effects in rats and mice and tracheobronchial effects in mice (Table A-2) were applied to the common duration-adjusted LOAEL of 1.25 ppm. The lowest human equivalent concentration was 0.1429 ppm for extrathoracic effects (hyperplasia of nasal respiratory epithelium) in female rats, which was selected as the point of departure for calculating the MRL since it would be protective against all effects.

Although a NOAEL was not available in this study, benchmark dose modeling was not performed to estimate an exposure level without appreciable risk because the data were not suitable. The group sizes were too small to model data sets for each sex separately, and the dose-response data for the combined sets provided no information as to the shape of the response curve below the tested exposure levels incidences for rats or mice with respiratory tract lesions increased from 0/10 in the control to 70–100% in the lowest exposure groups (Table A-1). For these reasons, the MRL was calculated using the NOAEL/LOAEL approach.

Was a conversion used from intermittent to continuous exposure? Yes. The LOAEL, 5 ppm, was adjusted for intermittent exposure (6 hours/24 hours), resulting in a duration-adjusted LOAEL of 1.25 ppm.

Other additional studies or pertinent information that lend support to this MRL: No data were available for the acute-duration inhalation toxicity of 2,3-dichloropropene in humans, and acute-duration inhalation data for animals, aside from the principal study, are limited to lethality studies (Dietz et al. 1985b; Monsanto 1967; Smyth et al. 1962; Union Carbide Corp. 1958). Exposure to an unquantified concentrated vapor of 2,3-dichloropropene resulted in effects on the eye (closure of eyelids, lacrimation), respiratory system (gasping, labored breathing, nasal discharge and, at necropsy, hemorrhagic lungs and inflammation of the nasal mucosa) and central nervous system (reduced activity, unconsciousness), and death within 30 minutes in rats (Monsanto 1967). An acute lethality inhalation study in rats reported no mortality at 250 ppm, 50% mortality at 500 ppm, and 100% mortality at 1,000 ppm after a 4-hour exposure (Smyth et al. 1962; Union Carbide Corp. 1958); this study provided no information about target organ specificity. In a 1-hour acute inhalation lethality study (for which even-numbered pages were missing), all rats exhibited irritant effects on the eye (lacrimation), respiratory tract (gasping, shallow respiration), gastrointestinal system (diarrhea), and central nervous system (lethargy) during exposure at concentrations of 693–1,963 ppm (Dietz et al. 1985b); postexposure lethargy and labored respiration were observed in rats exposed at 1,963 ppm. As described in Dietz et al. (1985b), results of a 6-hour range-finding inhalation study in rats included no overt toxicity at 75 ppm, crusted noses at 250 ppm, and

bloody noses, diarrhea, lethargy, and death at 500 ppm; irritation of the eyes and nose were named as the primary treatment-related effects in the range-finding study.

The limited database indicates that irritant effects, especially on the respiratory system, are the critical effects of acute-duration inhalation exposure to 2,3-dichloropropene. The study by Zempel et al. (1987) was selected as the principal study since it was adequately designed and reported, and it documented respiratory effects at the lowest tested concentration in rats and mice, providing reliable LOAELs for these effects.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,3-Dichloropropene
CAS Numbers: 542-75-6
Date: June 2008
Profile Status: Final Draft Post-public
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 20
Species: Mouse

Minimal Risk Level: 0.008 [ ] mg/kg/day [X] ppm

Reference: Lomax L, Stott W, Johnson K, et al. 1989. The chronic toxicity and oncogenicity of inhaled technical grade 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 12:418-431.

Experimental design: Groups (10/sex/concentration) of B6C3F1 mice and F344 rats were exposed to vapors of 1,3-dichloropropene 6 hours/day, 5 days/week for 6 months at concentrations of 0, 5, 20, or 60 ppm (0, 22.7, 90.8, or 272 mg/m^3). These were designed as interim satellite groups for a 2-year study. The test material was 92.1% pure (49.5% cis; 42.6% trans) and contained 2.0% epoxidized soybean oil (ESO) as a stabilizer, 0.7% 1,2-dichloropropane, and a calculated 5.2% mixtures of hexanes and hexadienes. Animals were observed after each exposure for clinical signs and moribund animals necropsied to minimize postmortem autolysis. Body weights were recorded before the study began, weekly for the first 13 weeks, and at monthly intervals thereafter. Urinalysis was conducted on rats during the week prior to termination; hematology and clinical chemistry parameters were analyzed in blood samples taken from rats and mice at the time of necropsy. All animals received examination by gross necropsy, at which time absolute and relative brain, heart, kidney, liver, and testicular weights were recorded. More than 40 tissues, in addition to gross lesions, were examined for histopathology in control and high-exposure animals at scheduled sacrifice and in all animals dying prematurely. About 17 tissues, in addition to gross lesions, were examined in low- and mid-exposure animals at scheduled termination.

Effects noted in study and corresponding doses: Exposure to 1,3-dichloropropene for 6 months had no adverse effect on survival, clinical signs, or hematological or clinical chemistry parameters in mice. Body weights of high-dose mice were depressed compared to controls, but the differences were not biologically significant at 6 months. Reductions in liver and kidney weights in males at 60 ppm were attributed by study authors to the reduced body weight and were not accompanied by histopathology. Statistically significant increased incidences of histopathological lesions were observed in mice treated at 60 ppm: hypertrophy/hyperplasia of the nasal respiratory epithelium in male and female mice and hyperplasia of the urinary bladder in female mice (Table A-3).

Table A-3. Incidence of Significant Lesions in B6C3F1 Mice Exposed to 1,3-Dichloropropene (92.1%) Vapor 6 Hours/Day, 5 Days/Week for 6 Months

	Control	22.7 mg/m^3 (5 ppm)	90.8 mg/m^3 (20 ppm)	272 mg/m^3 (60 ppm)
Slight hypertrophy/hyperplasia of nasal respiratory epithelium				
Male	1/10	0/10	3/10	10/10[a]
Female	0/10	0/10	0/10	7/10[a]
Hyperplasia of urinary bladder				
Male	0/10	0/10	0/10	1/10
Female	0/10	0/10	0/10	4/10[a]

[a]Different from control using Fisher Exact Test

Source: Lomax et al. 1989

Dose and end point used for MRL derivation: Hypertrophy/hyperplasia of nasal respiratory epithelium in male and female B6C3F1 mice exposed to 60 ppm (272 mg/m^3) 1,3-dichloropropene (92.1% purity), 6 hours/day, 5 days/week for 6 months was selected as the critical effect. Using benchmark concentration analysis, a $BMCL_{10}$ value of 1.0678 mg/m^3 was calculated for male mice and 13.5227 mg/m^3 was calculated for female mice (see Tables A-4 and A-6). Using EPA (1994) dosimetric adjustments, the male $BMCL_{10}$ value was converted to a human equivalent concentration ($[BMCL_{10}]_{HEC}$) of 1.0678 mg/m^3 (0.2349 ppm), which was selected as the point of departure for the MRL since it was lower than the female value. Note that concentrations in mg/m^3 were converted to ppm by using a factor of 0.22 (see Table 4-2 in this profile).

[ ] NOAEL [ ] LOAEL
[X] $[BMCL_{10}]$

Uncertainty Factors used in MRL derivation: 30 applied to the $[BMCL_0]_{HEC}$ of 0.2349 ppm for nasal effects in male mice

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans using dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Although 1,3-dichloropropene is a category 2 gas, the extrathoracic (ET) regional gas dose ratios (RGDRs) were calculated from rat and mouse data using the equation for a category 1 gas by default, since an equation is not available for category 2 gases. This is equation 4-18 in EPA (1994); in this section, all pages/equations/tables refer to EPA (1994).

$$RGDR_{ET} = (Dose_{ET})_{mouse} / (Dose_{ET})_{human} = (VE/SA_{ET})_{mouse} / (VE/SA_{ET})_{human}$$

The minute volumes (VE) for male and female mice were calculated using equation 4-4.
$LN(VE) = b_0 + b_1 [LN(BW \text{ in } kg)]$

Intercept b_0 of 0.326 and slope b_1 of 1.050 for mouse were taken from Table A-6.

The subchronic body weights of 0.0316 kg for male and 0.0246 kg for female B6C3F1 mice were taken from Table 4-5.

VE_{mouse}	= mouse minute volume (L/minute)	= 36.8353 mL/minute for male mice and 28.3168 mL/minute for females.
$(SA_{ET})_{mouse}$	= mouse surface area of extrathoracic region	= 3 cm^3, from Table A-4
VE_{human}	= human minute volume (L/minute)	= 13,800 mL/minute, from page 4-33
$(SA_{ET})_{human}$	= human surface area of extrathoracic region	= 200 cm^3, from Table A-4

Extrathoracic regional gas dose ratios were calculated as 0.1779 for male mice and 0.1368 for females exposed in an intermediate-duration study. These values were used to convert the respective male and female mouse BMCL values to human equivalent concentrations (see below).

Was a conversion used from intermittent to continuous exposure? Yes. The exposure concentrations (in mg/m^3 as reported by study authors) were adjusted by the purity of the compound (92.1%) and intermittent exposure (6 hours/24 hours x 5 days/7 days). Benchmark concentration analyses were conducted using these adjusted exposure levels.

Other additional studies or pertinent information that lend support to this MRL: In the only intermediate-duration inhalation study in humans, no evidence of renal or hepatic damage was detected in clinical chemistry analyses of blood and serum in pesticide applicators using cis-1,3-dichloropropene for an average of 521 (±230) minutes/day at a geometric mean concentration (8-hour TWA) of 2.7 mg/m^3 (range 0.1–9.5 mg/m^3) (0.594 [0.22–2.09] ppm) over a 117-day period compared to unexposed controls (Verplanke et al. 2000). No other end points were examined in this study. Respiratory effects (mucous membrane irritation, chest pain, cough, and breathing difficulties) have been observed following accidental acute exposure to high concentrations (Flessel et al. 1978; Markovitz and Crosby 1984).

The available data from the inhalation exposure animal studies indicate that hypertrophy/hyperplasia of the nasal respiratory epithelium and hyperplasia of the urinary bladder in mice are the most sensitive effects associated with intermediate-duration exposed to 1,3-dichloropropene. Increased incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium occurred in male and female B6C3F1 mice exposed to 60 ppm Telone II®b (92.1% 1,3-dichloropropene with 2% epoxidized soybean oil) vapor 6 hours/day, 5 days/week for 6 months (Lomax et al. 1989). Female mice in this study exposed at 60 ppm also had a marginally increased incidence of hyperplasia of the urinary bladder. Fischer 344 rats exposed in this study under the same protocol did not exhibit histopathology after 6 months exposure (Lomax et al. 1989). Slight reductions in body weights were observed in rats and mice exposed at 60 ppm, but the differences were not biologically significant (were <10% lower than controls) at 6 months (Lomax et al. 1989). Nasal lesions were also observed in rats exposed to ≥90 ppm Telone II®b 6 hours/day, 5–7 days/week for 3 months in a reproductive toxicity assay (Breslin et al. 1989). Nasal hyperplasia in rats and mice and urinary bladder hyperplasia in mice occurred in groups exposed to ≥90 ppm Telone II®a (90.9% 1,3-dichloropropene with 1.2% epichlorohydrin) 6 hours/day, 5 days/week for 13 weeks (Stott et al. 1988). One 13-week study by Coate (1979a) reported nasal lesions in rats exposed 6 hours/day, 5 days/week to Telone II®a at 30 ppm, but since the purity of the test material was not reported, the significance of the result is uncertain.

Although increased incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium and hyperplasia of the urinary bladder were both sensitive effects in mice at a LOAEL of 60 ppm, urinary hyperplasia was only observed in females and at a marginal increase (p=0.043; Fisher Exact Test) over

controls. Since the nasal lesions were observed in both sexes at a higher incidence, they were selected as the critical effect for development of the intermediate-duration MRL for 1,3-dichloropropene. The 6-month study with male and female mice exposed to Telone II®b by Lomax et al. (1989) was selected as the principal study because the study was adequately designed and reported, and because the test material contained a relatively high concentration of 1,3-dichloropropene without the confounding presence of epichlorohydrin or chloropicrin.

Potential points of departure for deriving the intermediate-duration MRL, derived with benchmark dose (concentration) analysis, are shown in Table A-4. Before the analysis, exposure concentrations in ppm were converted to mg/m^3 and adjusted for 92.1% purity and discontinuous exposure. Additional details of the benchmark dose (concentration) analysis are described below.

For increased incidence of hypertrophy/hyperplasia of nasal epithelium in male and female mice, the potential point of departure was the BMCL associated with 10% extra risk; this BMR is the default recommended in EPA (2000a).

Table A-4. Potential Points of Departure for Determining the Intermediate-duration Inhalation MRL for 1,3-Dichloropropene

End point	BMC[a] (mg/m^3)	BMCL[a] (mg/m^3)
Increased incidence of hypertrophy/hyperplasia of nasal respiratory epithelium in male and female mice exposed to Telone II®b vapor 6 hours/day, 5 days/week for 6 months	M 12.6179 F 28.7185	M 6.0022 F 13.5227
BMR = 10% extra risk		

[a]Adjusted for <100% purity and discontinuous exposure; To convert to ppm, multiply by 0.22

BMC = benchmark concentration; BMCL = 95% lower confidence limit for the benchmark concentration; BMR = benchmark response level; F = female; M = male; MRL = Minimal Risk Level

Source: Lomax et al. 1989

The mouse $BMCL_{10}$ values were multiplied by the extrathoracic regional dose ratios (mouse/human) (calculated above) for male and female B6C3F1 mice. The male $BMCL_{20}$ of 6.0022 mg/m^3 for hypertrophy/hyperplasia of nasal respiratory epithelium multiplied by an RGDR of 0.1779 results in a human equivalent concentration of 1.0678 mg/m^3 (0.2349 ppm). The female $BMCL_{10}$ of 13.5227 mg/m^3 for the same lesion multiplied by an RGDR of 0.1368 results in a human equivalent concentration of 1.8499 mg/m^3 (0.407 ppm). The lower value based on male mice was selected as the point of departure for MRL derivation because it would be more protective of human health. A total uncertainty factor of 30 was applied to the male $[BMCL_{10}]_{HEC}$ of 0.2349 ppm to calculate the intermediate-duration inhalation MRL for 1,3-dichloropropene.

The intermediate-duration inhalation MRL for 1,3-dichloropropene is based on the Lomax et al. (1989) study which used technical grade dichloropropene containing 92.1% 1,3-dichloropropene, 0.7% 1,2-dichloropropene, 2% epoxidized soybean oil as a stabilizer, and a calculated 5.2% mixture of hexanes and hexadienes. It is unlikely that hexane significantly contributed to the toxicity of 1,3-dichloropropene. Although hexane and 1,3-dichloropropene both affect the olfactory epithelium, the lowest LOAEL for this effect by n-hexane is almost 2 orders of magnitude higher than for 1,3-dichloropropene. As such, the hexane and hexadiene component is not considered to be a confounder in toxicity assessments for 1,3-dichloropropene.

Details of Benchmark Dose Analysis for the Intermediate-duration Inhalation MRL

Male and Female Mice:

All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for hypertrophy/hyperplasia of nasal respiratory epithelium in male and female B6C3F1 mice exposed to 1,3-dichloropropene via inhalation for 6 months (Table A-5). Predicted concentrations associated with 10, 5, and 1% extra risks were calculated.

Table A-5. Incidence of Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Male and Female B6C3F1 Mice Exposed 6 months, Adjusted for Purity and Discontinuous Exposure

Administered concentration		Adjusted for 92.1%	Adjusted for discontinuous	Incidence	
ppm	mg/m^3	purity (mg/m^3)	exposure and rounded (mg/m^3)	Males	Females
0	0	0	0	1/10	0/10
5	22.7	20.9067	3.7	0/10	0/10
20	90.8	83.6268	14.9	3/10	0/10
60	272	250.512	44.7	10/10	7/10

Source: Lomax et al. 1989

Hypertrophy/hyperplasia of nasal respiratory epithelium in male and female mice

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data (x^2 p-value ≥ 0.1) for the incidence of hypertrophy/hyperplasia of nasal respiratory epithelium in male (Table A-6) and female (Table A-7) B6C3F1 mice. Comparing across models, a better fit is indicated by a lower Akaike's Information Criteria value (AIC) (EPA 2000b). The gamma model was determined to be the best-fitting model for both males and females, as indicated by the AIC (Tables A-6 and A-7; Figures A-1 and A-2). Benchmark concentrations (BMCs and BMCLs) associated with an extra risk of 10, 5, and 1%, calculated from the best fitting model, are shown in Table A-8.

Table A-6. Goodness of Fit Statistics and BMC_{10}s and $BMCL_{10}$s from Models Fit to Incidence Data for Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Male B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 6 Months

Model	AIC	X^2 p-value[a]	BMC_{10} (mg/m^3)[b]	$BMCL_{10}$ (mg/m^3)[b]
Gamma[c]	**24.1579**	**0.5908**	**12.6179**	**6.00215**
Logistic	25.1526	0.3291	8.41841	5.1448
Log-Logistic	26.1579	0.3049	13.939	7.23456
Multistage	25.3494	0.4014	7.62026	3.9162
Probit	25.2768	0.3167	7.64022	4.69897
Log-probit	26.1579	0.3049	13.2999	6.97026

Table A-6. Goodness of Fit Statistics and BMC_{10}s and $BMCL_{10}$s from Models Fit to Incidence Data for Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Male B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 6 Months

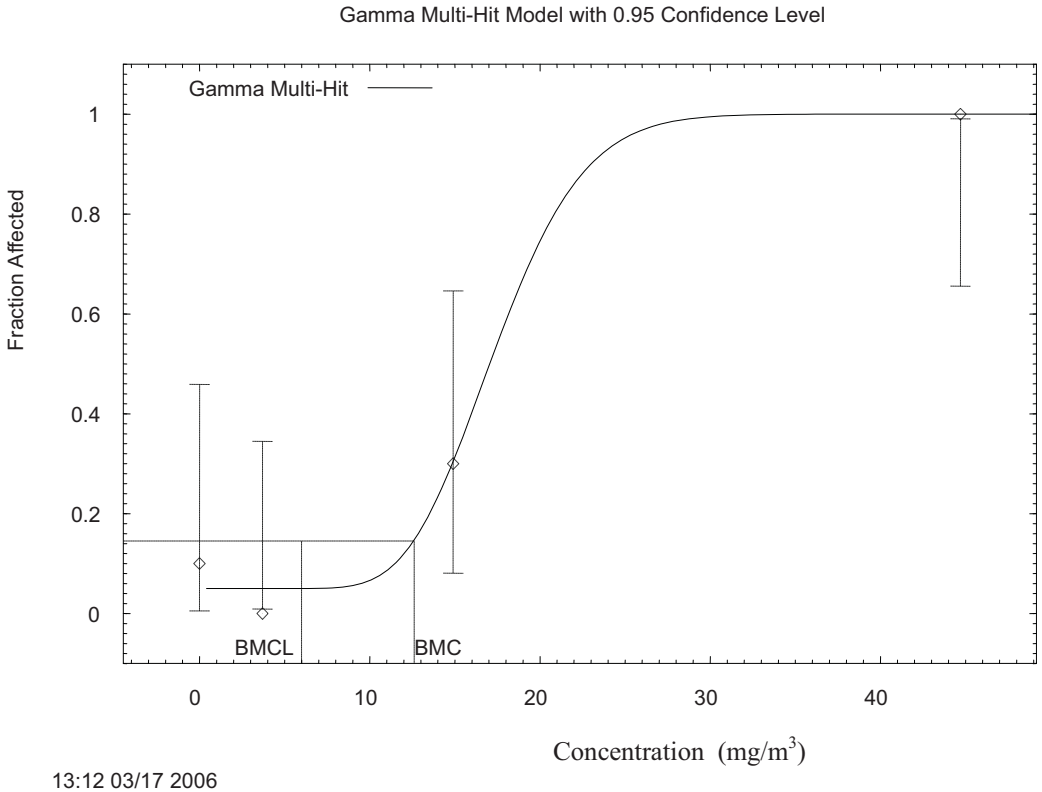
Model	AIC	X^2 p-value[a]	BMC_{10} (mg/m^3)[b]	$BMCL_{10}$ (mg/m^3)[b]
Quantal-linear	31.8559	0.0529	2.70925	1.64437
Quantal-quadratic	25.3494	0.4014	7.62026	5.43757
Weibull	26.1579	0.3049	13.1405	5.44413

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]To convert to ppm, multiply by 0.22.
[c]Best-fitting model

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; p = p-value from the Chi-squared test

Source: Lomax et al. 1989

Figure A-1. Observed and Predicted Incidences of Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Male B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 6 Months*



*BMCs and BMCLs indicated are for a 10% extra risk and are in units of mg/m^3.
BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration
Source: Lomax et al. 1989

The form and parameters of the gamma model for the male mouse data are as follows:

P[response]= background+(1-background)*CumGamma[slope*dose,power],
where CumGamma(.) is the cumulative Gamma distribution function

background = 0.0499995
slope = 1.01615
power = 18

Table A-7. Goodness of Fit Statistics and BMC_{10}s and $BMCL_{10}$s from Models Fit to Incidence Data for Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Female B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 6 Months

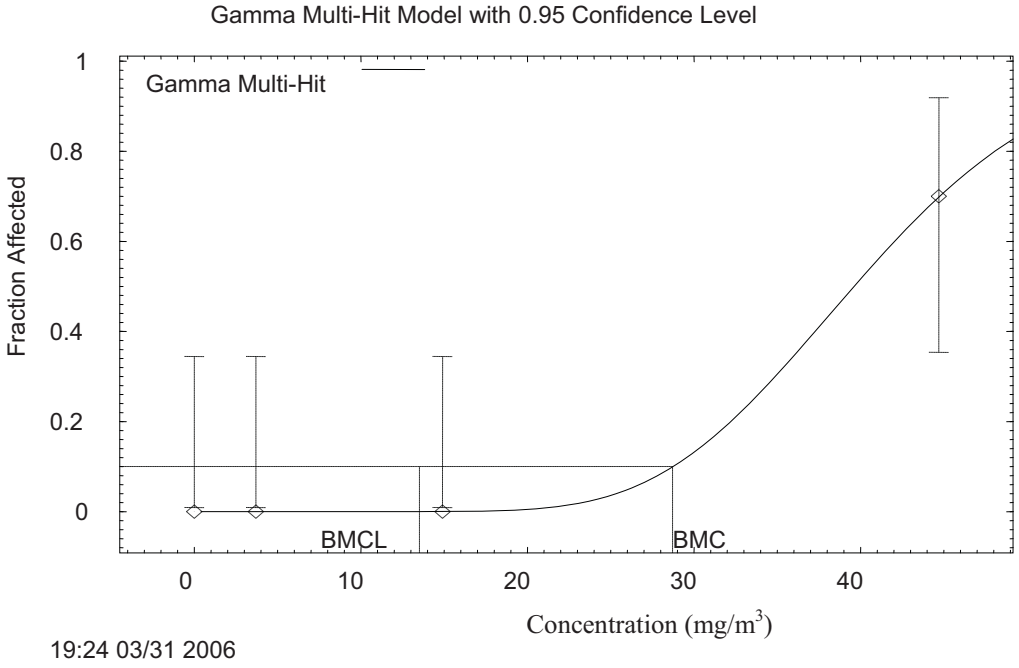
Model	AIC	X^2 p-value[a]	BMC_{10} (mg/m^3)[b]	$BMCL_{10}$ (mg/m^3)[b]
Gamma[c]	**14.2213**	**1.0000**	**28.7185**	**13.5227**
Logistic	16.2173	1.0000	40.0892	17.7767
Log-Logistic	16.2173	1.0000	37.7164	13.5983
Multistage	16.779	0.6925	14.6277	8.36083
Probit	16.2173	1.0000	35.9801	16.19
Log-probit	16.2173	1.0000	32.4372	13.6137
Quantal-linear	21.6296	0.1851	6.90725	3.87399
Quantal-quadratic	16.779	0.6925	14.6277	10.8645
Weibull	16.2173	1.0000	38.8344	13.5533

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]To convert to ppm, multiply by 0.22.
[c]Best-fitting model

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; p = p-value from the Chi-squared test

Source: Lomax et al. 1989

Figure A-2. Observed and Predicted Incidences of Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Female B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 6 Months*



*BMCs and BMCLs indicated are for a 10% extra risk and are in units of mg/m^3.
BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration

Source: Lomax et al. 1989

The form and parameters of the gamma model for the female mouse data are as follows:

P[response]=background+(1-background)*CumGamma[slope*dose,power],
where CumGamma(.) is the cumulative Gamma distribution function

background	=	0
slope	=	0.446459
power	=	18

Table A-8. Best-fitting Model Predictions for 1, 5, and 10% Extra Risk for Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Male and Female B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 6 Months

Best fitting model	BMR (percent extra risk)	BMC (mg/m^3)[a]	BMCL (mg/m^3)[a]
Male mice			
Gamma	1	9.46353	1.96448
	5	11.4494	4.23342
	10[b]	12.6179	6.00215
Female mice			
Gamma	1	21.5391	5.06945
	5	26.059	9.93499
	10	28.7185	13.5227

[a]To convert to ppm, multiply by 0.22.
[b]Best-fitting model
BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration;
BMR = benchmark response

Source: Lomax et al. 1989

Agency Contacts (Chemical Managers): Annette Ashizawa, Sharon Wilbur, and Heraline Hicks

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,3-Dichloropropene
CAS Numbers: 542-75-6
Date: June 2008
Profile Status: Final Draft Post-public
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 44
Species: Mouse

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

Reference: Lomax L, Stott W, Johnson K, et al. 1989. The chronic toxicity and oncogenicity of inhaled technical grade 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 12:418-431.

Experimental design: Groups (50/sex/concentration) of B6C3F1 mice and F344 rats were exposed to vapors of 1,3-dichloropropene 6 hours/day, 5 days/week for 2 years at concentrations of 0, 5, 20, or 60 ppm (0, 22.7, 90.8, or 272 mg/m^3). Additional satellite groups (10/sex/concentration) were established interim sacrifices at 6 and 12 months (results for the 6-month sacrifice are given under the description for the intermediate-duration inhalation MRL). The test material was 92.1% pure 1,3-dichloropropene (49.5% cis; 42.6% trans) and contained 2.0% ESO as a stabilizer, 0.7% 1,2-dichloropropane, and calculated 5.2% mixtures of hexanes and hexadienes. Animals were observed after each exposure for clinical signs, and moribund animals necropsied to minimize postmortem autolysis. Body weights were recorded before the study began, weekly for the first 13 weeks, and at monthly intervals thereafter. Urinalysis was conducted on rats during the week prior to termination; hematology and clinical chemistry parameters were analyzed in blood samples taken from rats and mice at the time of necropsy. All animals received examination by gross necropsy, at which time absolute and relative brain, heart, kidney, liver, and testicular weights were recorded. More than 40 tissues, in addition to gross lesions, were examined for histopathology in control and high-exposure animals at scheduled sacrifice and in all animals dying prematurely. About 17 tissues, in addition to gross lesions, were examined in low- and mid-exposure animals at scheduled termination.

Effects noted in study and corresponding doses: Exposure to Telone II®b vapor for 2 years had no significant adverse effect on survival, body weight, the incidence of clinical signs, hematology, or clinical chemistry parameters in mice. In the 1-year satellite group, incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium were significantly higher than controls in males at ≥20 ppm and in females at 60 ppm; females at 60 ppm also had increased incidences of epithelial hyperplasia and inflammation of the urinary bladder. Significant lesions observed in mice after 2 years of exposure are given in Table A-9. Nasal and urinary bladder lesions were elevated in males at 60 ppm and in females at ≥20 ppm. Increases in inflammation of the urinary bladder were not observed in males and were relatively small in females. Degeneration of the nasal olfactory epithelium was not statistically elevated in either sex at concentrations lower than 60 ppm. Hypertrophy/hyperplasia of the nasal respiratory epithelium and epithelial hyperplasia of the urinary bladder in females at ≥20 ppm were the most sensitive effects in this study.

Table A-9. Incidence of Significant Lesions in B6C3F1 Mice Exposed to 1,3-Dichloropropene (92.1%) Vapor 6 Hours/Day, 5 Days/Week for 2 Years

	Control	22.7 mg/m^3 (5 ppm)	90.8 mg/m^3 (20 ppm)	272 mg/m^3 (60 ppm)
Hypertrophy/hyperplasia of nasal respiratory epithelium (slight)				
Male	5/50	1/50	4/50	48/50[a]
Female	4/50	4/50	28/50[a]	49/50[a]
Degeneration of nasal olfactory epithelium (slight)				
Male	1/50	0/50	1/50	48/50[a]
Female	0/50	0/50	1/50	45/50[a]
Hyperplasia of urinary bladder (slight-moderate)				
Male	4/48	7/48	11/48	37/47[a]
Female	1/47	4/46	21/48[a]	44/45[a]
Inflammation of urinary bladder (slight-severe)				
Male	0/48	0/48	0/48	2/47
Female	0/47	1/46	6/48[a]	8/45[a]

[a]Statistically different from control

Source: Lomax et al. 1989

Dose and end point used for MRL derivation: Hypertrophy/hyperplasia of nasal respiratory epithelium in female B6C3F1 mice exposed at a LOAEL of 20 ppm (272 mg/m^3) 1,3-dichloropropene (92.1% purity), 6 hours/day, 5 days/week for 2 years. Using benchmark concentration analysis, $BMCL_{10}$ value of 4.5673 mg/m^3 was calculated (see Tables A-10 and A-15), and a human equivalent concentration ($[BMCL_{10}]_{HEC}$) of 0.9130 mg/m^3 (0.2009 ppm) was calculated using EPA (1994) dosimetric adjustments. Note that concentrations in mg/m^3 were converted to ppm by using a factor of 0.22 (see Table 4-2 in this profile).

[ ] NOAEL [ ] LOAEL
[X] [$BMCL_{10}$]

Uncertainty Factors used in MRL derivation: 30 applied to the $[BMCL_{10}]_{HEC}$ of 0.2009 ppm for nasal effects in female B6C3F1 mice

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

0.2009 ppm / 30 = 0.0067, rounded to 0.007 ppm

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Although 1,3-dichloropropene is a category 2 gas, the extrathoracic (ET) regional gas dose ratios (RGDRs) were calculated from rat and mouse data using the equation for a category 1 gas by default, since an equation is not available for category 2 gases EPA (1994).

$RGDR_{ET} = (Dose_{ET})_{mouse} / (Dose_{ET})_{human} = (VE/SA_{ET})_{mouse} / (VE/SA_{ET})_{human}$

The minute volumes (VE) for female mice were calculated using the equation
$LN(VE) = b_0 + b_1 [LN(BW \text{ in } kg)]$.
Intercept b_0 of 0.326, slope b_1 of 1.050 for mouse, and chronic body weight of 0.0353 kg for chronic female B6C3F1 mice were taken from (EPA 1994).

VE_{mouse}	= mouse minute volume (L/minute)	= 41.3741 mL/minute for chronic female mice
$(SA_{ET})_{mouse}$	= mouse surface area of extrathoracic region	= 3 cm^3
VE_{human}	= human minute volume (L/minute)	= 13,800 mL/minute
$(SA_{ET})_{human}$	= human surface area of extrathoracic region	= 200 cm^3

An extrathoracic regional gas dose ratio of 0.1999 was calculated for female mice exposed in a chronic-duration study. These values were used to convert the female mouse BMCL value for nasal lesions to a human equivalent concentration (see below).

Since epithelial hyperplasia of the urinary bladder is an extrarespiratory effect, the conversion to a human equivalent concentration is calculated for a category 3 gas using the ratio of animal/human blood:gas partition coefficients. However, as no blood:gas partition coefficients for 1,3-dichloropropene were located in the published literature, the default ratio of 1 is applied. The human equivalent $BMCL_{10}$ values are unchanged from the mouse values.

Was a conversion used from intermittent to continuous exposure? Yes. The exposure concentrations (in mg/m^3 as reported by study authors) were adjusted for the purity of the compound (92.1%) and intermittent exposure (6 hours/24 hours x 5 days/7 days). Benchmark concentration analyses were conducted using these adjusted exposure levels.

Other additional studies or pertinent information that lend support to this MRL: No data are available for effects in humans following chronic-duration inhalation exposure to 1,3-dichloropropene. Fischer F344 rats and B6C3F1 mice were evaluated for chronic-duration inhalation exposure to Telone II®b (92.1% 1,3-dichloropropene stabilized with 2% epoxidized soybean oil) for 1 or 2 years (Lomax et al. 1989).

The available data from chronic-duration studies indicate that lesions of the nasal epithelium and urinary bladder in mice are the most sensitive effects associated with chronic-duration inhalation exposure to 1,3-dichloropropene. After 1 year, incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium were increased in male mice exposed at ≥20 ppm and in female mice at 60 ppm. In addition, the incidences of hyperplasia and inflammation of the urinary bladder were increased in female mice exposed to 60 ppm for 1 year. After 2 years of exposure, increased incidences of hypertrophy/hyperplasia of the nasal respiratory epithelium occurred in female mice at ≥20 ppm and males exposed at 60 ppm, and increased degeneration of the nasal olfactory epithelium occurred in male and female mice exposed at 60 ppm. In rats, nasal lesions were only detected at 60 ppm after 2 years of exposure and at lower incidences than in exposed mice: decreased thickness of the olfactory epithelium in males and females, erosion of the olfactory epithelium in males, and submucosal fibrosis in males. The incidences of epithelial hyperplasia of the urinary bladder were increased in female mice exposed for 2 years at ≥20 ppm and male mice exposed at 60 ppm; the incidence of inflammation of the bladder epithelium was

increased in female mice exposed for 2 years at ≥20 ppm, but not in males. No histopathology of the urinary bladder was observed in rats.

Based on these findings, hypertrophy/hyperplasia of the nasal respiratory epithelium and hyperplasia of the urinary bladder epithelium in mice exposed for 2 years were selected as co-critical effects for development of the chronic-duration inhalation MRL for 1,3-dichloropropene. The mouse study by Lomax et al. (1989) is accepted as the principal study because the test material in this adequately designed and reported study had a purity of 92.1% and did not contain epichlorohydrin or chloropicrin as a possibly confounding toxic additive.

Potential points of departure for deriving the chronic-duration inhalation MRL using benchmark concentration analysis are shown in Table A-10. Before the analysis, exposure concentrations in ppm were converted to mg/m^3, and adjusted for 92.1% purity and discontinuous exposure. Additional details of the benchmark concentration analysis are described below. None of the models in the EPA BMD software provided an adequate fit to the data for hypertrophy/hyperplasia of the nasal respiratory epithelium in male mice, so no BMCL could be calculated. For increased incidence of hypertrophy/hyperplasia of nasal respiratory epithelium in female mice or hypertrophy of urinary bladder epithelium in male and female mice, the potential points of departure were the 95% lower confidence limits on estimated concentrations ($BMCL_{10}$s) associated with 10% extra risk compared to control values. This benchmark response (BMR) level is the default recommended by EPA (2000a).

Table A-10. Potential Points of Departure for Determining the Chronic-duration Inhalation MRL for 1,3-Dichloropropene

End point	BMC_{10}[a] (mg/m^3)[b]	$BMCL_{10}$[a] (mg/m^3)[b]
Hypertrophy/hyperplasia of nasal respiratory epithelium (slight) in B6C3F1 mice exposed to Telone II®b vapor for 2 years	M[c] F 7.0833	M[c] F 4.5673
BMR = 10% extra risk		
Hyperplasia of urinary bladder (slight-moderate) in B6C3F1 mice exposed to Telone II®b vapor for 2 years	M 9.9024 F 6.9087	M 8.0838 F 5.9079
BMR = 10% extra risk		

[a]Adjusted for <100% purity and discontinuous exposure
[b]To convert to ppm, multiply by 0.22.
[c]No models provided adequate fits to the data.

BMC = benchmark concentration; BMCL = 95% lower confidence limit for the benchmark concentration; BMR = benchmark response level

Source: Lomax et al. 1989

Mouse BMCL values were converted to human equivalent concentrations using EPA (1994) dosimetry methods. The $BMCL_{10}$ of 4.5673 mg/m^3 for hypertrophy/hyperplasia of nasal respiratory epithelium in female mice was multiplied by the extrathoracic regional dose ratio (mouse/human) of 0.1999 (calculated above), resulting in a human equivalent concentration of 0.9130 mg/m^3 (0.2009 ppm). The default ratio of 1 was applied for calculating the human equivalent concentrations for the extrarespiratory effects and urinary bladder lesions, resulting in values unchanged from those of male and female mice: respectively, 8.0838 and 5.9079 mg/m^3 (1.7784 and 1.2997 ppm).

The $[BMCL_{10}]_{HEC}$ value of 0.2009 ppm for hypertrophy/hyperplasia of nasal respiratory epithelium in female mice was selected as the more sensitive point of departure for the chronic-duration inhalation MRL for 1,3-dichloropropene.

The chronic-duration inhalation MRL for 1,3-dichloropropene is based on the Lomax et al. (1989) study which used technical grade dichloropropene containing 92.1% 1,3-dichloropropene, 0.7% 1,2-dichloropropene, 2% epoxidized soybean oil as a stabilizer, and a calculated 5.2% mixture of hexanes and hexadienes. It is unlikely that hexane significantly contributed to the toxicity of 1,3-dichloropropene. Although hexane and 1,3-dichloropropene both affect the olfactory epithelium, the lowest LOAEL for this effect by n-hexane is almost 2 orders of magnitude higher than for 1,3-dichloropropene. As such, the hexane and hexadiene component is not considered to be a confounder in toxicity assessments for 1,3-dichloropropene.

Details of Benchmark Dose Analysis for the Chronic-duration Inhalation MRL

Male and Female Mice:

All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for hypertrophy/hyperplasia of nasal respiratory and urinary bladder epithelium in male and female B6C3F1 mice exposed to 1,3-dichloropropene via inhalation for 2 years (Table A-11). Predicted concentrations associated with 10, 5, and 1% extra risks were calculated.

Table A-11. Incidence of Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium and Urinary Bladder Epithelium in Male and Female B6C3F1 Mice Adjusted for Purity and Discontinuous Exposure

	Administered concentration (mg/m^3)[a]	Concentration adjusted for 92.1% purity and for discontinuous exposure (mg/m^3)[a]	Incidence	
			Males	Females
Nasal respiratory epithelium	0	0	5/50	4/50
	22.7	3.7	1/50	4/50
	90.8	14.9	4/50	28/50
	272	44.7	48/50	49/50
Urinary bladder epithelium	0	0	4/48	1/47
	22.7	3.7	7/48	4/46
	90.8	14.9	11/48	21/48
	272	44.7	37/47	44/45

[a]To convert to ppm, multiply by 0.22.

Source: Lomax et al. 1989

Hypertrophy/hyperplasia of nasal respiratory epithelium in male and female mice

As assessed by the chi-square goodness-of-fit test, no models in the software provided adequate fits to the data for the incidence of hypertrophy/hyperplasia of nasal respiratory epithelium in male B6C3F1 mice since all of the chi-square p-values were lower than 0.1 (data not shown). Several models in the software provided adequate fits to the data for the incidence of for hypertrophy/hyperplasia of nasal respiratory epithelium in female B6C3F1 mice (x^2 p-value ≥0.1) (Table A-12). Comparing across models, a better fit is indicated by a lower AIC (EPA 2000b). The log-probit model was determined to be the best-fitting model for the female data, as indicated by the AIC (Table A-12). Benchmark concentrations (BMCs and BMCLs) associated with an extra risk of 10, 5, and 1%, calculated from the best fitting model, are shown in Table A-15.

Table A-12. Goodness of Fit Statistics and BMC_{10}s and $BMCL_{10}$s from Models Fit to Incidence Data for Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Female B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 2 Years

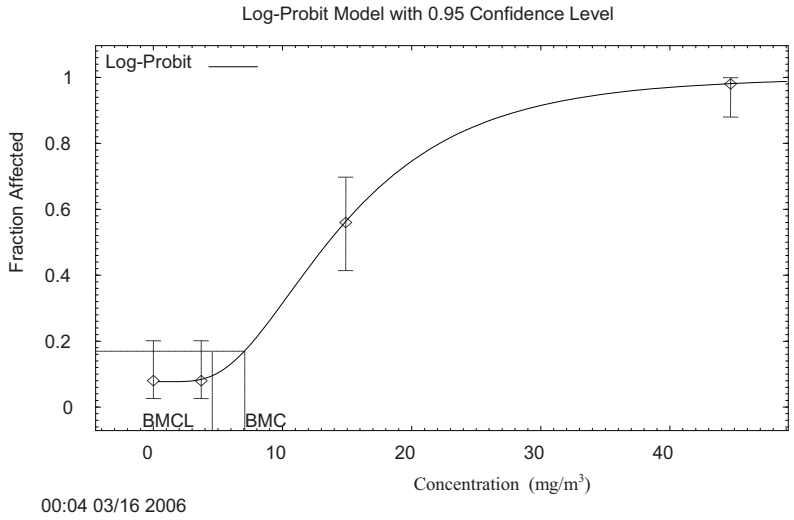
Model	AIC	X^2 p-value[a]	BMC_{10} (mg/m^3)[b]	$BMCL_{10}$ (mg/m^3)[b]
Gamma	140.696	0.4605	5.88054	3.64206
Logistic	141.091	0.1720	5.39501	4.3506
Log-Logistic	140.177	0.8712	7.6296	4.86553
Multistage	142.702	0.1047	4.9972	2.62038
Probit	142.872	0.0716	5.19777	4.23194
Log-probit[c]	**140.166**	**0.9004**	**7.08327**	**4.56728**
Quantal-linear	150.075	0.0082	1.90984	1.53078
Quantal-quadratic	141.085	0.1307	6.30223	5.39173
Weibull	141.736	0.2167	4.94384	3.13411

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]To convert to ppm, multiply by 0.22.
[c]Best-fitting model

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; p = p-value from the Chi-squared test

Source: Lomax et al. 1989

Figure A-3. Observed and Predicted Incidences of Hypertrophy/Hyperplasia of Nasal Respiratory Epithelium in Female B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 2 Years*



*BMCs and BMCLs indicated are for a 10% extra risk and are in units of mg/m^3.
BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration

Source: Lomax et al. 1989

The form and parameters of the log-probit model for the female mouse nasal lesion data are as follows:

P[response] = Background+ (1-Background)* CumNorm(Intercept+Slope*Log(Dose)),

where CumNorm(.) is the cumulative normal distribution function

background	=	0.0769028
intercept	=	-4.80042
slope	=	1.79742

Slight/moderate hyperplasia of urinary bladder epithelium in male and female mice

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data (x^2 p-value $\geq$0.1) for the incidence of for slight/moderate hyperplasia of urinary bladder epithelium in male (Table A-13; Figure A-4) and female (Table A-14; Figure A-5) B6C3F1 mice. Comparing across models, a better fit is indicated by a lower AIC (EPA 2000b). The logistic model was determined to be the best fitting model for the male data (Table A-13), whereas the quantal quadratic model was determined to be the best-fitting model for the female data (Table A-14), as indicated by the AIC. Benchmark concentrations (BMCs and BMCLs) associated with an extra risk of 10, 5, and 1%, calculated from the best fitting models for both sexes, are shown in Table A-15.

Table A-13. Goodness of Fit Statistics and BMC_{10}s and $BMCL_{10}$s from Models Fit to Incidence Data for Slight/Moderate Hyperplasia of Urinary Bladder Epithelium in Male B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 2 Years

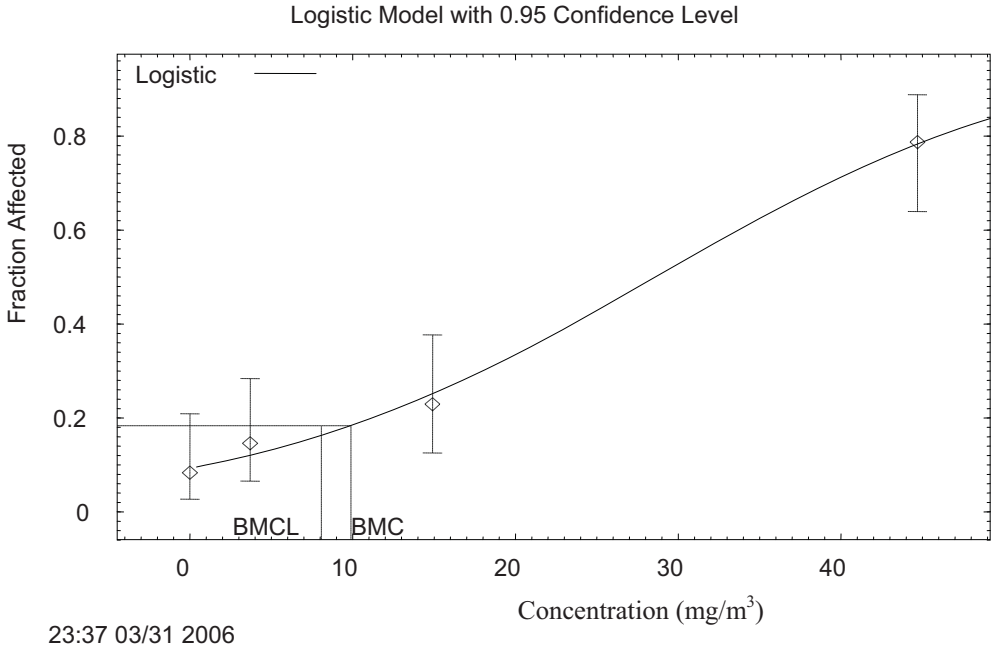
Model	AIC	X^2 p-value[a]	BMC_{10} (mg/m^3)[b]	$BMCL_{10}$ (mg/m^3)[b]
Gamma	174.596	0.3561	12.9064	5.9353
Logistic[c]	**172.196**	**0.7929**	**9.90241**	**8.08381**
Log-Logistic	174.593	0.3576	13.1008	7.37023
Multistage	174.403	0.4119	10.9233	4.95677
Probit	172.305	0.7515	9.13794	7.58289
Log-probit	174.671	0.3380	13.5586	8.28718
Quantal-linear	177.633	0.0631	4.15472	3.1987
Quantal-quadratic	172.465	0.6951	12.1536	10.4772
Weibull	174.465	0.3939	12.1787	5.68456

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]To convert to ppm, multiply by 0.22.
[c]Best-fitting model

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; p = p-value from the Chi-squared test

Source: Lomax et al. 1989

Figure A-4. Observed and Predicted Incidences of Slight/Moderate Hyperplasia of Urinary Bladder Epithelium in Male B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 2 Years*



*BMCs and BMCLs indicated are for a 10% extra risk and are in units of mg/m^3.
BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration

Source: Lomax et al. 1989

The form and parameters of the logistic model for the male mouse data are as follows:

P[response] = 1/[1+EXP(-intercept-slope*dose)]

background	=	0 (Specified)
intercept	=	-2.19615
slope	=	0.0769886

Table A-14. Goodness of Fit Statistics and BMC_{10}s and $BMCL_{10}$s from Models Fit to Incidence Data for Slight/Moderate Hyperplasia of Urinary Bladder Epithelium in Female B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 2 Years

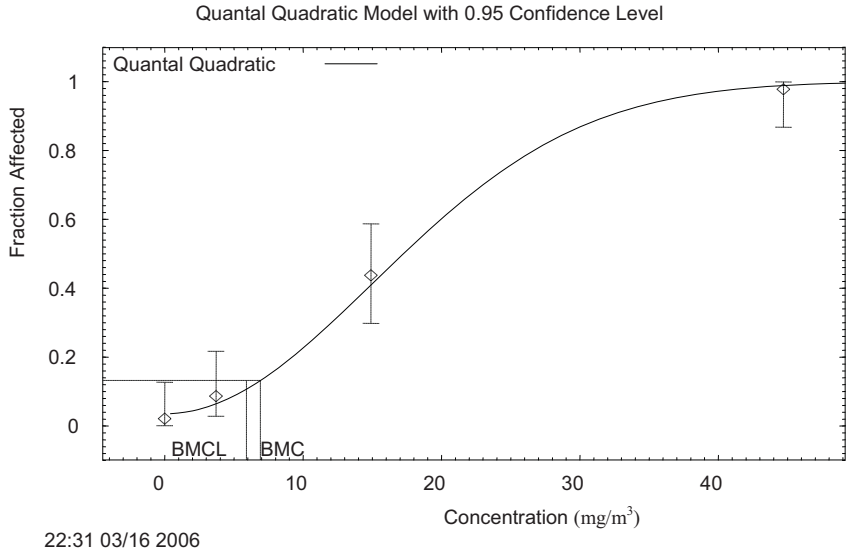
Model	AIC	X^2 p-value[a]	BMC_{10} (mg/m^3)[b]	$BMCL_{10}$ (mg/m^3)[b]
Gamma	119.054	0.3665	5.94769	3.5405
Logistic	118.133	0.3632	6.93667	5.55287
Log-Logistic	120.1	0.1816	8.84738	5.10377
Multistage	118.241	0.9777	4.99209	2.90579
Probit	118.606	0.2979	6.62106	5.3209
Log-probit	120.27	0.1657	8.76593	4.86738
Quantal-linear	126.03	0.0206	2.16273	1.72952
Quantal-quadratic[c]	**117.42**	**0.5326**	**6.90872**	**5.90793**
Weibull	118.378	0.7085	5.4465	3.42639

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]To convert to ppm, multiply by 0.22.
[c]Best-fitting model

AIC = Akaike's Information Criteria; BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; p = p-value from the Chi-squared test

Source: Lomax et al. 1989

Figure A-5. Observed and Predicted Incidences of Slight/Moderate Hyperplasia of Urinary Bladder Epithelium in Female B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 2 Years*



*BMCs and BMCLs indicated are for a 10% extra risk and are in units of mg/m^3.
BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration

Source: Lomax et al. 1989

The form and parameters of the quantal-quadratic model for the female mouse data are as follows:

P[response] = background + (1-background)*[1-EXP(-slope*dose^2)]

background = 0.03125
slope = 0.00169733
power = 2 (Specified)

Table A-15. Best-fitting Model Predictions for 1, 5, and 10% Extra Risk for Hypertrophy/Hyperplasia of Nasal Respiratory in Female and Urinary Bladder Epithelium in Male and Female B6C3F1 Mice Exposed to 1,3-Dichloropropene via Inhalation for 2 Years

Best fitting model	BMR (percent extra risk)	BMC (mg/m^3)[a]	BMCL (mg/m^3)[a]
Male mice[b]			
Urinary bladder epithelium: quantal quadratic	1	1.30075	0.988608
	5	5.65321	4.47585
	10	9.90241	8.08381
Female mice			
Nasal respiratory epithelium: Log-Probit	1	3.96085	2.0326
	5	5.78698	3.45244
	10[c]	7.08327	4.56728
Urinary bladder epithelium: quantal quadratic	1	2.13378	1.82468
	5	4.82046	4.12218
	10	6.90872	5.90793

BMC = benchmark concentration; BMCL = lower confidence limit (95%) on the benchmark concentration; BMR = benchmark response

[a]To convert to ppm, multiply by 0.22.
[b]No models provided adequate fits for the incidence data for nasal lesions in male mice.
[c]Best-fitting model

Source: Lomax et al. 1989

Agency Contacts (Chemical Managers): Annette Ashizawa, Sharon Wilbur, and Heraline Hicks

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,3-Dichloropropene
CAS Numbers: 542-75-6
Date: June 2008
Profile Status: Final Draft Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 10
Species: Rat

Minimal Risk Level: 0.04 [X] mg/kg/day [ ] ppm

Reference: Haut KT, Stebbins KE, Johnson KA, et al. 1996. Subchronic toxicity of ingested 1,3-dichloropropene in rats and mice. Fundam Appl Toxicol 32:224-232.

Experimental design: Haut et al. (1996) exposed groups of male and female Fischer 344 rats (10/sex/group) to 1,3-dichloropropene at doses of 0, 5, 15, 50, or 100 mg/kg/day for 13 weeks. The test material, Telone II®b, was 95.8% pure 1,3-dichloropropene (50.7% cis; 45.1% trans) stabilized with epoxidized soybean oil, and was microencapsulated in a starch/sucrose (80:20) microsphere matrix before addition to the diets; separate tests showed that the microencapsulated compound was stable in feed for at least three weeks, but test diets were mixed fresh weekly. Control diets received empty microspheres in an amount equivalent to the high-dose treated group. Animals were examined daily for clinical signs of toxicity and received a weekly clinical examination. Body weights and feed intake were recorded prior to testing and weekly during the study. For rats, urinalysis was conducted during the week before the scheduled necropsy and at necropsy, blood samples were collected for hematology and clinical chemistry evaluations. At necropsy, absolute and relative organ weights were recorded for brain, liver, kidneys, heart, and adrenals. Samples of 65 tissues from all rats were preserved and those of the control and high-dose groups were examined for histopathology; gross lesions and tissues from five organs (lung, liver, kidney, stomach, female mesenteric tissues) from low- and mid-dose animals were scheduled for histopathological examination.

Effects noted in study and corresponding doses: Treatment with 1,3-dichloropropene had no adverse effect on survival in rats. Body weights were significantly reduced by 16% in male rats treated at 50 mg/kg/day and by 11% in female rats treated at 100 mg/kg/day; statistically significant reductions in body weights at lower doses were not biologically significant. The study authors indicated that significantly reduced feed intake at the high doses likely contributed to the reduced body weights, as well as the slightly reduced absolute organ weights and increased relative organ weights. The authors attributed minor changes in clinical chemistry parameters in rats (e.g., reduction in triglycerides) to the poorer nutritional status of high-dose rats.

A NOAEL of 5 mg/kg/day and a LOAEL of 15 mg/kg/day were identified for minimal basal cell hyperplasia of the nonglandular stomach in male rats treated at 15 mg/kg/day and female rats at 50 mg/kg/day (Table A-16). Female rats at 100 mg/kg/day also exhibited hyperkeratosis of the nonglandular stomach. These lesions represent portal-of-entry effects from ingested 1,3-dichloropropene.

Table A-16. Incidence of Histopathological Lesions of Basal Cells in the Nonglandular Stomach in F344 Rats Exposed to 1,3-Dichloropropene (Telone II®b) in the Diet for 13 Weeks

	Dose (doses in mg/kg/day; group size = 10)				
	0	5	15	50	100
Hyperplasia					
Males	0	0	4[a]	10[a]	10[a]
Females	0	0	3	10[a]	10[a]
Hyperkeratosis					
Males	0	0	1	3	3
Females	0	0	0	3	5[a]

[a]Statistically different from control, Fisher Exact Test performed by Syracuse Research Corporation.

Source: Haut et al. 1996

Dose and end point used for MRL derivation: Minimal hyperplasia of the nonglandular stomach mucosa in male Fischer 344 rats treated at 15 mg/kg/day for 13 weeks. The calculated $BMDL_{10}$ value of 3.5722 mg/kg/day (see Table A-17) was used as the point of departure for the MRL

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in MRL derivation: 100 applied to the $BMDL_{10}$ of 3.5722 mg/kg/day for increased incidence of forestomach basal cell hyperplasia in male rats

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

3.5722 mg/kg/day / 100 = 0.0357, rounded to 0.04 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Study authors reported doses as calculated from feed intake.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable. Intake was *ad libitum*.

Other additional studies or pertinent information that lend support to this MRL: No data are available for effects in humans following intermediate-duration oral exposure to 1,3-dichloropropene. Intermediate-duration oral exposure studies with rats, mice, and dogs exposed to different commercial formulations of 1,3-dichloropropene isomers have been conducted by oral gavage or dietary exposure.

The available data from the oral exposure animal studies indicate that lesions in the nonglandular stomach mucosa in rats and microcytic anemia in dogs are the most sensitive effects associated with intermediate-duration oral exposure to 1,3-dichloropropene (see Chapter 3 for more detailed discussion of health effects associated with 1,3-dichloropropene). Increased incidences of basal cell hyperplasia of the

nonglandular stomach occurred in male Fischer 344 rats exposed to doses ≥15 mg/kg/day Telone II®b microencapsulated in feed for 13 weeks; female rats displayed hyperkeratosis of the nonglandular stomach epithelium at doses of 100 mg/kg/day in this study (Haut et al. 1996). B6C3F1 mice exposed to Telone II®b via the same protocol for 13 weeks did not display any adverse effects on histologic or hematologic end points (Haut et al. 1996). Microcytic anemia (decreased hematocrit, hemoglobin concentration, and corpuscular volume) occurred in beagle dogs exposed to doses ≥15 mg/kg/day Telone II®b encapsulated in feed for 13 weeks (Stebbins et al. 1999). Reductions in terminal body weight were observed in rats, mice, and dogs exposed to Telone II®b in feed for 13 weeks, but reduced food intake associated with decreased palatability may have contributed to these effects (Haut et al. 1996; Stebbins et al. 1999). In an earlier 13-week study with Telone®, a commercial formulation of lesser 1,3-dichloropropene purity than Telone II®b, increased liver or kidney weights were observed in rats at doses as low as 10 and 30 mg/kg/day, respectively, but the lack of renal or kidney adverse noncancer effects in the intermediate- or chronic-duration studies with Telone II®b suggests that these organs are not consistently observed noncancer toxicity targets of 1,3-dichloropropene.

Basal cell hyperplasia in the nonglandular stomach of male rats and decreased hemoglobin concentration and corpuscular volume in male or female dogs were sensitive effects occurring at the same exposure levels. However, the intermediate-duration study in dogs by Stebbins et al. (1999) was judged to be inadequate as a critical study because no histopathology examination was conducted and the group sizes were small. Therefore, basal cell hyperplasia in the nonglandular stomach of male rats was selected as the critical effect for development of the intermediate-duration MRL for 1,3-dichloropropene. The 13-week study with male rats (Haut et al. 1996) exposed to microencapsulated Telone II®b was selected as the principal study, because the test material in these adequately designed and reported studies was the most purified 1,3-dichloropropene formulation tested and did not contain potentially confounding toxic materials such as epichlorohydrin or chloropicrin.

Potential points of departure for deriving the intermediate-duration MRL, derived with benchmark dose analysis, are shown in Table A-17. Details of the benchmark dose analyses are given below.

Table A-17. Potential Points of Departure for Determining the Intermediate-duration Oral MRL for 1,3-Dichloropropene

End point	BMD (mg/kg/day)	BMDL (mg/kg/day)
Increased incidence of basal cell hyperplasia of nonglandular stomach mucosa in male rats exposed to Telone II®b in feed for 13 weeks (Haut et al. 1996) BMR = 10% extra risk	9.0030	3.5722

BMD = benchmark dose; BMDL = 95% lower confidence limit for the benchmark dose; BMR = benchmark response level; MRL = Minimal Risk Level

For increased incidence of basal hyperplasia in nonglandular stomach mucosa of rats, the potential point of departure was the BMDL associated with 10% extra risk; this BMR was the default recommended in EPA (2000a).

An intermediate-duration oral MRL of 0.04 mg/kg/day was derived by dividing the rat $BMDL_{10}$ of 3.5722 mg/kg/day for basal cell hyperplasia by a composite uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The MRL is based on the Haut et al. (1996) study which used Telone II®b containing 95.8% 1,3-dichloropropene with no other constituents reported.

Details of Benchmark Dose Analysis for the Intermediate-duration Oral MRL

Male Rats:

All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for basal cell hyperplasia of nonglandular stomach mucosa in male rats exposed to 1,3-dichloropropene in the diet for 13 weeks (Table A-18). Predicted doses associated with 10, 5, and 1% extra risks were calculated (Table A-20).

Table A-18. Incidence of Basal Cell Hyperplasia of Nonglandular Stomach Mucosa (minimal) in Fisher 344 Rats Exposed to 1,3-Dichloropropene in the Diet for 13 Weeks

	Doses in mg/kg body weight/day				
	Control	5	15	50	100
Males	0/10	0/10	4/10[a]	10/10[a]	10/10[a]

[a]Statistically different from control (Fisher Exact Test performed by SRC March 2006)

Source: Haut et al. 1996

Male Rats:

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of basal cell hyperplasia of nonglandular stomach mucosa in male rats (x^2 p-value $\geq$0.1) (Table A-19). Comparing across models, a better fit is indicated by a lower AIC (EPA 2000b). A 3-degree polynomial multi-stage model was determined to be the best-fitting model, as indicated by the AIC (Table A-19; Figure A-6). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 10, 5, and 1%, calculated from the best fitting model, are shown in Table A-20.

Table A-19. Goodness of Fit Statistics and BMD_{10}s and $BMDL_{10}$s from Models Fit to Incidence Data for Basal Cell Hyperplasia of Nonglandular Stomach Mucosa in Male Rats Exposed to 1,3-Dichloropropene in the Diet for 13 Weeks

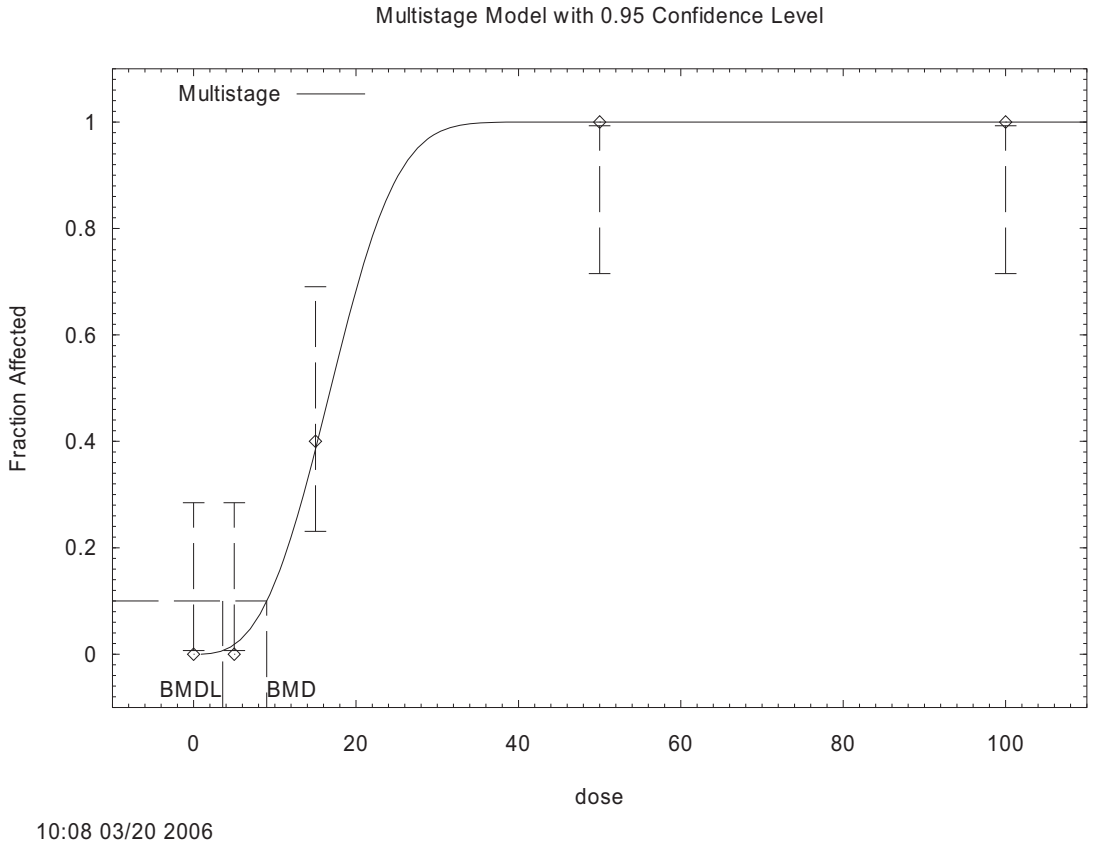
Model	AIC	X^2 p-value[a]	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma	15.4607	1.0000	11.5681	5.1935
Logistic	17.4602	1.0000	14.0398	6.8305
Log-Logistic	17.4602	1.0000	13.5206	6.25073
Multistage[b]	**15.8298**	**0.9957**	**9.00298**	**3.57217**
Probit	17.4602	1.0000	13.1012	6.25656
Log-probit	17.4602	1.0000	12.213	5.92308
Quantal-linear	22.7351	0.3922	2.40324	1.53389
Quantal-quadratic	16.6383	0.9616	7.05272	5.01843
Weibull	17.4612	1.0000	12.4316	4.82232

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Best-fitting model

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not applicable; p = p-value from the Chi-squared test

Source: Haut et al. 1996

Figure A-6. Observed and Predicted Incidences of Basal Cell Hyperplasia of Nonglandular Stomach Mucosa in Male Rats Exposed to 1,3-Dichloropropene in the Diet for 13 Weeks*



*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.
BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: Haut et al. 1996

The form and parameters of the multi-stage model for the male rat data are as follows:

P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2-beta3*dose^3)]

background	=	0
Beta(1)	=	0
Beta(2)	=	0
Beta(3)	=	0.000144384

Table A-20. Best-fitting Model Predictions for 1, 5, and 10% Extra Risk for Basal Cell Hyperplasia of Nonglandular Stomach Mucosa in Male Rats Exposed to 1,3-Dichloropropene in the Diet for 13 Weeks

Best fitting model	BMR (% extra risk)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male: Multistage	1	4.11358	0.416759
	5	7.0824	1.76019
	10	9.00298	3.57217

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; BMR = benchmark response

Source: Haut et al. 1996

Agency Contacts (Chemical Managers): Annette Ashizawa, Sharon Wilbur, and Heraline Hicks

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,3-Dichloropropene
CAS Numbers: 542-75-6
Date: June 2008
Profile Status: Final Draft Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 18
Species: Rat

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

References: Co-principal studies:

Stebbins KE, Johnson KA, Jeffries TK, et al. 2000. Chronic toxicity and oncogenicity studies of ingested 1,3-dichloropropene in rats and mice. Regul Toxicol Pharmacol 32:1-13.

Stebbins KE, Quast JF, Haut KT, et al. 1999. Subchronic and chronic toxicity of ingested 1,3-dichloropropene in dogs. Regul Toxicol Pharmacol 30:233-243.

Experimental design: Stebbins et al. (2000) exposed groups of male and female Fischer 344 rats (50/sex/group) to 1,3-dichloropropene in the diet at doses of 0, 2.5, 12.5, or 25 mg/kg/day for 2 years; satellite groups of 10/sex/group were scheduled for interim sacrifice at 12 months. Stebbins et al. (1999) exposed beagle dogs (4/sex/group) to dose of 0, 0.5, 2.5, or 15 mg/kg/day for 1 year. In both studies, the test material, Telone II®b, was 95.8% pure 1,3-dichloropropene (50.7% cis; 45.1% trans) with 2% ESO as a stabilizer and was microencapsulated in a starch/sucrose (80:20) microsphere matrix before addition to the diets; separate tests showed that the microencapsulated compound was stable in feed for at least three weeks, but test diets were mixed fresh weekly. Control diets received empty microspheres in an amount equivalent to that given to the high-dose treated group. Animals were examined daily for clinical signs of toxicity and received a weekly clinical examination. Body weights and feed intake were recorded prior to testing and weekly during the first 13 weeks of the study and at monthly intervals thereafter. For rats, urinalysis samples and blood samples for hematology and clinical chemistry and were obtained from the satellite groups at 6 and 12 months and from survivors in the main group at 18 months (10 animals/sex/group) and 24 months (20 animals/sex/group). For dogs, blood samples were collected prior to testing and after 3, 6, and 9 months of dosing and during the week prior to termination; urine samples were taken from dogs at necropsy. At necropsy, absolute and relative organ weights were recorded for brain, liver, kidneys, testes, ovaries, heart, and adrenals in both species and for thyroids plus parathyroids in dogs. Complete sets tissues from all animals were preserved and, in rats, those of the control and high-dose groups and animals dying prematurely were examined for histopathology; gross lesions and tissues from selected organs (lung, liver, uterus, kidney, stomach, and testes) from low- and mid-dose animals were scheduled for histopathological examination. All dogs were examined for histopathology in the full range of tissues.

Effects noted in study and corresponding doses: Both studies: Dietary exposure to Telone II®b had no effect on survival in rats exposed for 2 years or dogs exposed for 1 year.

Rats:

Body weights of high-dose male and female rats were 15–16% lower than controls, but feed consumption was also reduced by 12–13%. Exposure had no significant effect on hematology, clinical chemistry, or

urinalysis parameters. Reduced triglyceride counts in high-dose males and females were attributed by the authors to the decreased body weights, rather than a toxicological response.

In rats, the most sensitive effect of exposure after 2 years was basal cell hyperplasia of the nonglandular stomach mucosa observed in male and female rats exposed at 12.5 or 25 mg/kg/day (Table A-21). The incidence of this lesion was also significantly elevated in the satellite group after 1 year of exposure in males at 12.5 mg/kg/day and in females at 25 mg/kg/day. The incidence of hepatic foci of any type was not increased with treatment, but treated rats showed increases of eosinophilic foci compared to basophilic foci. The incidence of benign hepatocellular adenomas was significantly increased in male rats at 25 mg/kg/day (incidence 2/50, 1/50, 6/50, 9/50), whereas females showed a positive trend for these tumors (incidence 0/50, 0/50, 0/50, 4/50). One male rat treated at 25 mg/kg/day had a hepatic carcinoma.

Table A-21. Incidence of Histopathological Lesions of Basal Cells in the Nonglandular Stomach in F344 Rats Exposed to 1,3-Dichloropropene (Telone II®b) in the Diet for 2 Years

	Dose (doses in mg/kg/day; group size = 50)			
	0	2.5	12.5	25
Hyperplasia				
Males	3	3	20[a]	30[a]
Females	0	1	20[a]	37[a]

[a]Statistically different from controls

Source: Stebbins et al. 2000

Dogs:

Terminal body weights were significantly lower than controls by 11% in male dogs and 15% in female dogs exposed at 15 mg/kg/day. Exposure had no effect on feed consumption or urinalysis results. The study authors indicated that changes in clinical chemistry parameters were not associated with histopathology in any organ. In dogs, the most sensitive effects were reductions in hemoglobin, hematocrit, and mean corpuscular volume, all characteristic of microcytic anemia observed in dogs at a LOAEL of 15 mg/kg/day (Table A-22); the NOAEL was 2.5 mg/kg/day in dogs.

Table A-22. Hematological Effects in Beagle Dogs Exposed to 1,3-Dichloropropene (Telone II®b) in the Diet for 1 Year

	Dose (doses in mg/kg/day; group size = 4/sex/dose)			
	0	0.5	2.5	15
Hemoglobin (g/dL)				
Males	17.4±1.6	17.5±1.0	13.7±1.3	12.3±3.1[a]
Females	17.3±2.1	17.1±1.2	18.0±0.6	12.6±1.2[a]
Hematocrit (%)				
Males	57.0±4.1	56.6±3.0	55.7±1.4	40.5±10.4[a]
Females	57.3±5.7	56.6±3.4	60.4±2.8	40.9±3.5[a]
Mean corpuscular volume (fL)				
Males	73±1	72±2	69±4	44±4[a]
Females	75±3	73±2	72 ±3	43±5[a]

[a]Statistically different from control

Source: Stebbins et al. 1999

Dose and end point used for MRL derivation: Basal cell hyperplasia of the nonglandular stomach mucosa observed in female rats exposed at a LOAEL of 12.5 mg/kg/day for 2 years. BMDL values were calculated for these and other effects (see Table A-23). If the $BMDL_{10}$ value of 3.5124 mg/kg/day for female rats was used as the point of departure, the derived MRL would be 0.04 mg/kg/day. This is in agreement with the EPA (2000a) chronic oral RfD of 0.03 mg/kg/day based on a $BMDL_{10}$ of 3.4 mg/kg/day for the same data. Therefore, EPA's $BMDL_{10}$ of 3.4 mg/kg/day was selected as the point of departure for the chronic-duration oral MRL.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{10}$

Uncertainty Factors used in MRL derivation: 100 applied to EPA's $BMDL_{10}$ of 3.4 mg/kg/day for increased incidence of forestomach basal cell hyperplasia in female rats.

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

3.4 mg/kg/day / 100 = 0.034, rounded to 0.03 mg/kg/day

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. Study authors reported doses based on feed intake data.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable. Intake was *ad libitum*.

Other additional studies or pertinent information that lend support to this MRL: No data are available for effects in humans following chronic-duration oral exposure to 1,3-dichloropropene. Chronic-duration oral exposure studies with rats, mice, and dogs exposed to different commercial formulations of 1,3-dichloropropene isomers have been conducted by oral gavage or dietary exposure.

As with the animal data for intermediate-duration exposure, the available data indicate that lesions in the nonglandular stomach mucosa in rats and microcytic anemia in dogs are the most sensitive effects associated with chronic-duration oral exposure to 1,3-dichloropropene (see Chapter 3 for a more detailed discussion of health effects associated with 1,3-dichloropropene). Basal cell hyperplasia of the nonglandular stomach mucosa was observed in male and female Fischer 344 rats exposed to doses as low as 12.5 mg/kg/day Telone II®b (but not 2.5 mg/kg/day) encapsulated in feed for 1 or 2 years (Stebbins et al. 2000), and in male and female F344 rats and female B6C3F1 mice exposed to gavage doses of 25 mg/kg/day Telone II®a (89% dichloropropene isomers plus 1% epichlorohydrin) 3 times/week for up to 2 years (NTP 1985). Increased incidences of this lesion did not occur in male or female B6C3F1 mice exposed to 2.5, 25, or 50 mg/kg/day Telone II®b encapsulated in feed for 1 or 2 years (Stebbins et al. 2000) or in male or female beagle dogs exposed to 0.5, 2.5, or 15 mg/kg/day Telone II®b encapsulated in feed for 1 year (Stebbins et al. 1999). However, male and female beagle dogs exposed to 15 mg/kg/day, but not 2.5 mg/kg/day, Telone II®b encapsulated in feed for 1 year showed decreased values for mean hematocrit, hemoglobin concentration, and corpuscular volume, compared with control values, which are indicative of microcytic anemia. Exposure-related reductions in terminal body weight were observed in rats, mice, and dogs exposed to Telone II®b in feed for 1 or 2 years, but reduced food intake associated with decreased palatability may have contributed to these effects (Stebbins et al. 1999, 2000).

Adverse noncancer effects on the liver or kidney are not as clearly associated with chronic-duration oral exposure to 1,3-dichloropropene as forestomach basal cell hyperplasia in rats or microcytic anemia in dogs. Exposure-related kidney effects include increased incidence of hydronephrosis in female, but not male, B6C3F1 mice exposed to gavage doses of 100 mg/kg/day Telone II®a , but not 50 mg/kg/day, for up to 2 years (NTP 1985) and increased incidence of nephropathy in female, but not male, Fischer 344 rats exposed to 25 or 50 mg/kg/day Telone II®a for up to 2 years (NTP 1985). However, no exposure-related kidney effects were observed in Fischer 344 rats, B6C3F1 mice, or beagle dogs exposed to Telone II®b encapsulated in feed for 1 or 2 years at doses as high as 25 mg/kg/day for rats, 50 mg/kg/day for mice, and 15 mg/kg/day for dogs (Stebbins et al. 1999; 2000). Observed noncancer effects in the liver include decreased size of hepatocytes in male, but not female, B6C3F1 mice exposed to 50 mg/kg/day, but not 25 mg/kg/day, Telone II®b encapsulated in feed for 1 year, but not in mice exposed for 2 years (Stebbins et al. 2000) and increased incidence of slight or very slight eosinophilic foci of altered liver cells in male and female Fischer 344 rats exposed to 2.5, 12.5, or 25 mg/kg/day Telone II®b encapsulated in feed for 2 years. The toxicological significance of these apparent liver effects is equivocal given the inconsistency of the findings in the mouse study and the common spontaneous occurrence of liver foci (eosinophilic or basophilic) in aged Fischer 344 rats.

Based on the findings from the chronic-duration oral exposure animal studies, basal cell hyperplasia in the nonglandular stomach of male rats and decreased hemoglobin concentration and corpuscular volume in male or female dogs were selected as co-critical effects for development of the chronic-duration MRL for 1,3-dichloropropene. The 2-year rat study (Stebbins et al. 2000) and 1-year dog study (Stebbins et al. 1999) involving exposure to microencapsulated Telone II®b were selected as the principal studies, because the test material in these adequately designed and reported studies was the most purified 1,3-dichloropropene formulation tested (95.8% pure 1,3-dichloropropene—50.7% cis; 45.1% trans—with 2% epoxidized soybean oil as a stabilizer) and did not contain potentially confounding toxic materials such as epichlorohydrin or chloropicrin.

Potential points of departure for deriving the chronic-duration MRL, derived with benchmark dose analysis, are shown in Table A-23. Additional details of the benchmark dose analysis are described below.

For decreased hemoglobin concentration, which was as an index of 1,3-dichloropropene-induced microcytic anemia in dogs, potential points of departure were 95% lower confidence limits on estimated doses (i.e., BMDLs) associated with a value lower than 10th percentile values for the distribution of hemoglobin concentrations in a sample of normal beagle dogs (Table A-23).

Table A-23. Potential Points of Departure for Determining the Chronic-duration Oral MRL for 1,3-Dichloropropene

End point	BMD (mg/kg/day)	BMDL (mg/kg/day)
Decreased hemoglobin concentration in beagle dogs exposed to Telone II®b in feed for 1 year (Stebbins et al. 1999). BMR = 10th percentile hemoglobin concentrations in normal beagle dogs, age >1year: 14.6 mg/dL males (n=169) and 14.1 mg/dL females (n=185) (Wolford et al. 1986).	M 8.3455 F 10.978	M 6.0453 F 8.8294
Increased incidence of basal cell hyperplasia of nonglandular stomach mucosa in Fischer 344 rats exposed to Telone II®b in feed for 2 years (Stebbins et al. 2000) BMR = 10 % extra risk	M 5.3432 F 5.4209	M 4.2568 F 3.5124

BMD = benchmark dose; BMDL = 95% lower confidence limit for the benchmark dose; BMR = benchmark response level; F = female; M = male

For increased incidence of basal hyperplasia in nonglandular stomach mucosa of rats, the potential point of departure was the BMDL associated with 10% extra risk. This benchmark response (BMR) level is the default recommended by EPA (2000a).

The lowest BMDL, the $BMDL_{10}$ of 3.5124 mg/kg/day for increased incidence of nonglandular stomach basal cell hyperplasia in female rats, was selected as the point of departure for deriving the chronic-duration oral MRL since it should be protective against all effects.

A chronic-duration oral MRL of 0.04 mg/kg/day was derived by dividing the $BMDL_{10}$ of 3.5124 mg/kg/day for basal cell hyperplasia of the forestomach in female rats by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The MRL is based on the Stebbins et al. (1999, 2000) studies which used approximately 96% 1,3-dichloropropene with 2% epoxidized soybean oil as a stabilizer; no other constituents were reported.

Details of Benchmark Dose Analysis for the Chronic-duration Oral MRL

Male and Female Rats:

All available dichotomous models in the EPA Benchmark Dose Software (BMDS version 1.3.2) were fit to the incidence data for basal cell hyperplasia of nonglandular stomach mucosa in male rats, female rats, and combined male and female rats exposed to 1,3-dichloropropene in the diet for 2 years (Table A-24). Predicted doses associated with 10, 5, and 1 extra risks were calculated.

Table A-24. Incidence of Basal Cell Hyperplasia of Nonglandular Stomach Mucosa (Slight or Very Slight) in Fisher 344 Rats Exposed to 1,3-Dichloropropene in the Diet for 2 Years

	Control	2.5 mg/kg/day	12.5 mg/kg/day	25 mg/kg/day
Males	3/50	3/50	20/50	30/50
Females	0/50	1/50	20/50	37/50
Both sexes	3/100	4/100	40/100	67/100

Male Rats:

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of basal cell hyperplasia of nonglandular stomach mucosa in male rats (x^2 p-value ≥0.1) (Table A-25). Comparing across models, a better fit is indicated by a lower AIC (EPA 2000b). The log-probit model was determined to be the best-fitting model, as indicated by the AIC (Table A-25; Figure A-9). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 10, 5, and 1%, calculated from the best fitting model, are shown in Table A-27.

Table A-25. Goodness of Fit Statistics and BMD_{10}s and $BMDL_{10}$s from Models Fit to Incidence Data for Basal Cell Hyperplasia of Nonglandular Stomach Mucosa in Male Rats Exposed to 1,3-Dichloropropene in the Diet for 2 Years

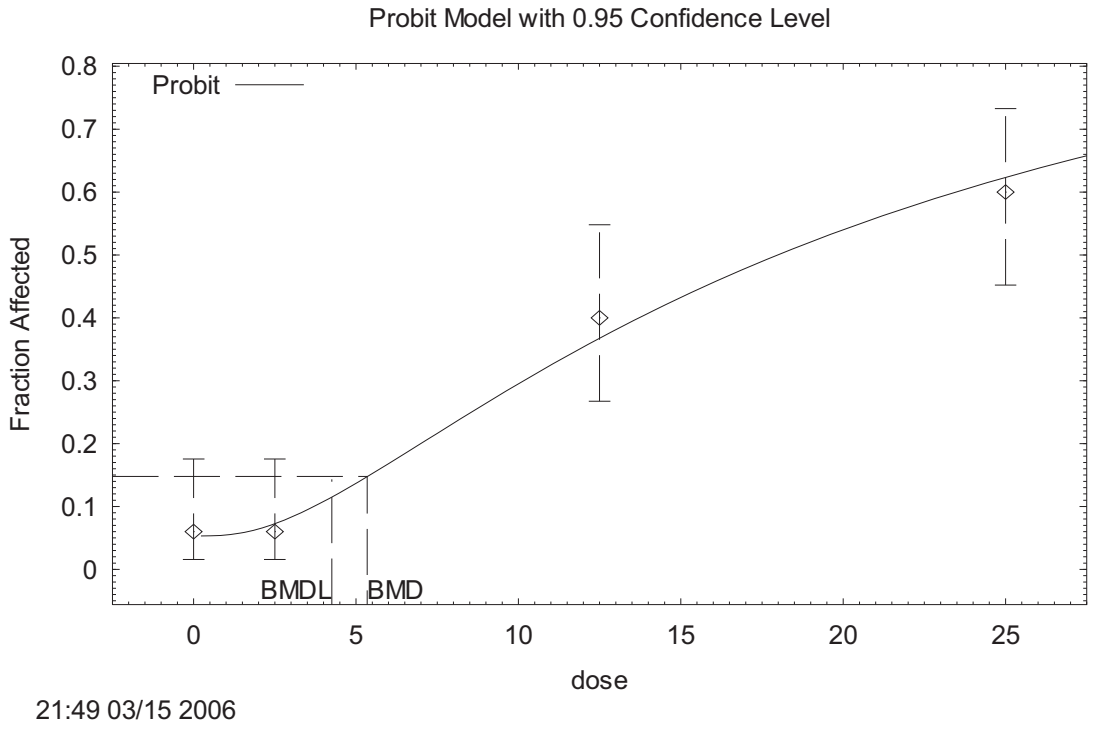
Model	AIC	X^2 p-value[a]	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma	187.302	0.2589	4.89969	2.57775
Logistic	189.052	0.0784	7.13438	5.92049
Log-Logistic	186.872	0.3554	4.96556	2.47384
Multistage	188.102	0.1603	4.06715	2.46921
Probit	188.191	0.1202	6.62804	5.54609
Log-probit[b]	**184.503**	**0.7769**	**5.34316**	**4.25684**
Quantal-linear	186.563	0.3216	3.09733	2.41788
Quantal-quadratic	188.62	0.0871	7.96066	6.94702
Weibull	187.529	0.2243	4.63368	2.54375

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Best-fitting model

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not applicable; p = p-value from the Chi-squared test

Source: Stebbins et al. 2000

Figure A-7. Observed and Predicted Incidences of Basal Cell Hyperplasia of Nonglandular Stomach Mucosa in Male Rats Exposed to 1,3-Dichloropropene in the Diet for 2 Years*



*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.
BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: Stebbins et al. 2000

The form and parameters of the log-probit model for the male rat data are as follows:

P[response] = Background+ (1-Background)* CumNorm(Intercept+Slope*Log(Dose)),

where CumNorm(.) is the cumulative normal distribution function

background	=	0.0531859
intercept	=	-2.95737
slope	=	1

Female Rats:

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of basal cell hyperplasia of nonglandular stomach mucosa in female rats (x^2 p-value $\geq$0.1) (Table A-26). Comparing across models, a better fit is indicated by a lower AIC (EPA 2000b). The log-logistic model was determined to be the best-fitting model, as indicated by the AIC (Table A-26; Figure A-8). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 10, 5, and 1%, calculated from the best fitting model, are shown in Table A-27.

Table A-26. Goodness of Fit Statistics and BMD_{10}s and $BMDL_{10}$s from Models Fit to Incidence Data for Basal Cell Hyperplasia of Nonglandular Stomach Mucosa in Female Rats Exposed to 1,3-Dichloropropene in the Diet for 2 Years

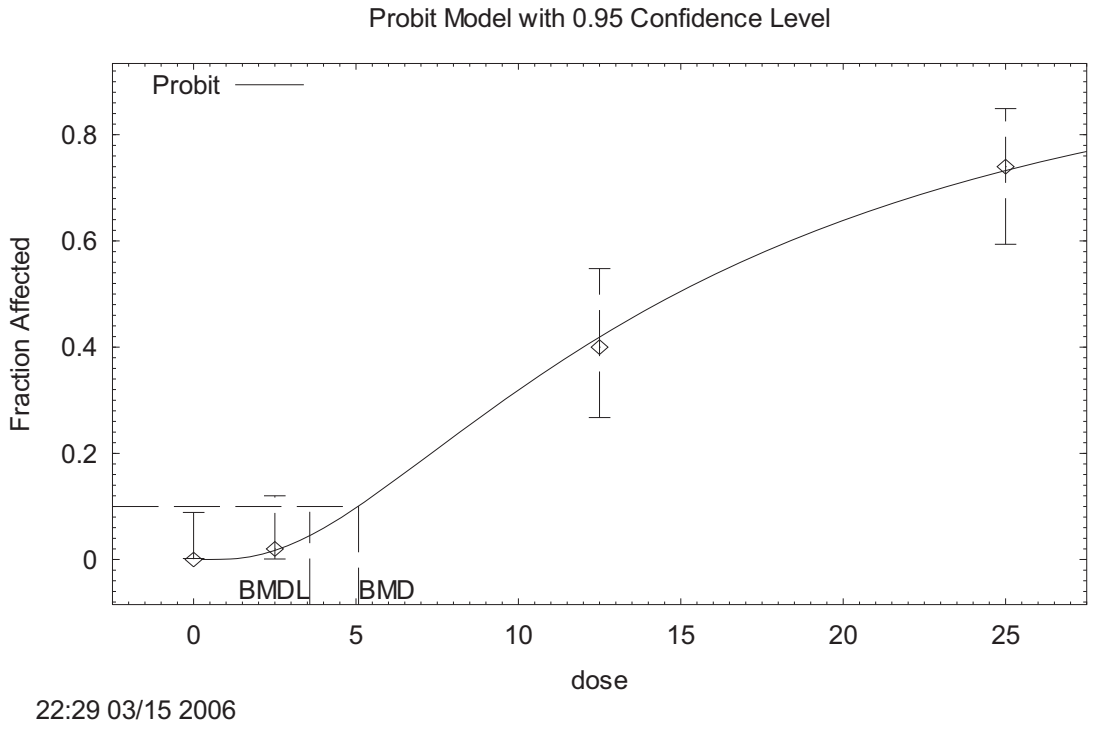
Model	AIC	X^2 p-value[a]	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Gamma	138.598	0.9121	5.25023	3.31605
Logistic	148.131	0.0176	7.67354	6.23867
Log-Logistic[b]	**138.416**	**0.9973**	**5.4209**	**3.51236**
Multistage	139.663	0.5468	5.29306	2.91991
Probit	145.812	0.0404	7.31771	5.93502
Log-probit	138.52	0.9461	5.07542	3.57721
Quantal-linear	143.267	0.1648	2.39166	1.92514
Quantal-quadratic	138.493	0.5372	6.49982	5.81197
Weibull	139.013	0.7530	5.08921	3.1648

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Best-fitting model

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; NA = not applicable; p = p-value from the Chi-squared test

Source: Stebbins et al. 2000

Figure A-8. Observed and Predicted Incidences of Basal Cell Hyperplasia of Nonglandular Stomach Mucosa in Female Rats Exposed to 1,3-Dichloropropene in the Diet for 2 Years*



*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.
BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: Stebbins et al. 2000

The form and parameters of the log-logistic model for the female rat data are as follows:

P[response] = background+(1-background)/[1+EXP(-intercept-slope*Log(dose))]

background	=	0
intercept	=	-5.8536
slope	=	2.14828

Table A-27. Best-fitting Model Predictions for 1, 5, and 10% Extra Risk for Basal Cell Hyperplasia of Nonglandular Stomach Mucosa in Male and Female Rats Exposed to 1,3-Dichloropropene in the Diet for 2 Years

Best fitting model	BMR (% extra risk)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male: Log-Probit	1	2.10426	1.25833
	5	3.7369	2.48751
	10	5.34316	4.25684
Female: Log-logistic	1	1.13014	0.258277
	5	3.13078	1.23116
	10	5.4209	3.51236

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; BMR = benchmark response

Source: Stebbins et al. 2000

Male and Female Dogs:

The linear model in the EPA Benchmark Dose Software (BMDS version 1.3.2) was fit to the data (Table A-28) for decreased hemoglobin concentration in beagle dogs exposed to 1,3-dichloropropene in the diet for 1 year. The linear model was selected as it is the simplest model available in the BMD software which adequately fits the hemoglobin concentration data. Hemoglobin concentration was selected as the most clearly adverse variable associate with 1,3-dichloropropene-induced microcytic anemia. BMDs and BMDLs associated with a value lower than the 10^{th} percentile value for hemoglobin in normal beagle dogs were calculated (Table A-29, Figures A-9 and A-10). The 10^{th} percentile hemoglobin concentrations in normal beagle dogs, age >1 year for the 1-year exposure were 14.6 mg/dL for males and 14.1 mg/dL for females (Wolford et al. 1986).

Table A-28. Hemoglobin Concentrations in Male and Female Beagle Dogs Exposed for 1 Year

Dose mg/kg/day	Male mean hemoglobin concentration ± standard deviation (g/dL)	Female Mean hemoglobin concentration ± standard deviation (g/dL)
0	17.4±1.6	17.3±2.1
0.5	17.5±1.0	17.1±1.2
2.5	13.7±1.3	18.0±0.6
15	12.3±3.1*	12.6±1.2*

Source: Stebbins et al. 1999

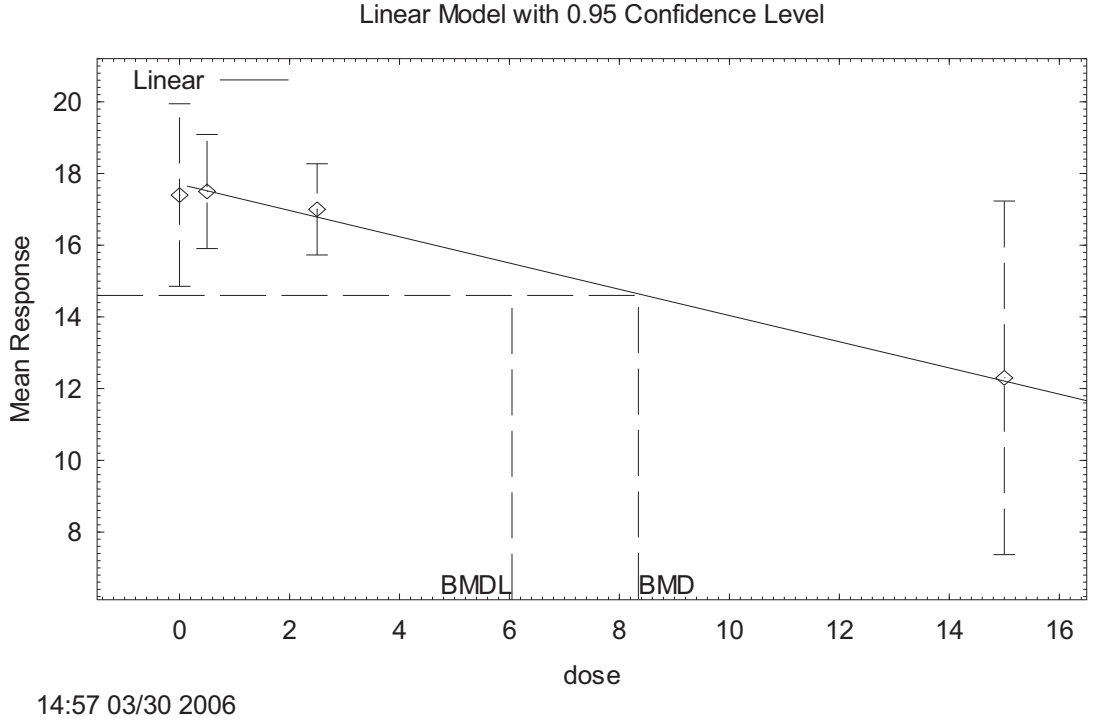
Table A-29. Linear Model Predictions for the Dose Associated with the 10th Percentile Value for Hemoglobin Concentration in Normal Beagle Dogs with the 95% Lower Confidence Limit

Data-set	$BMD_{10th\%ile}$ (mg/kg/day)	$BMDL_{10th\%ile}$ (mg/kg/day)
Chronic		
Male[a]	8.3455	6.04528
Female	10.978	8.82939

[a]Nonhomogeneous variance model

BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

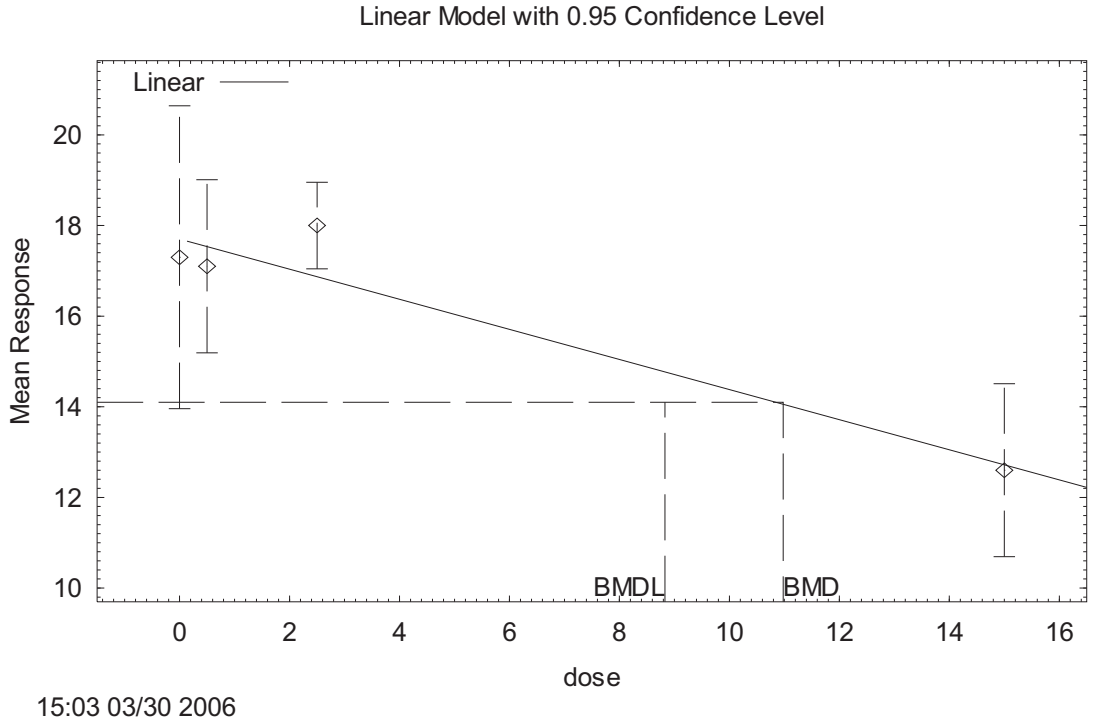
Figure A-9. Linear (Nonhomogeneous Variance) Model Predicted Change in Hemoglobin Concentration in Male Beagle Dogs Exposed to 1,3-Dichloropropene in the Diet for 1 Year*



*BMDs and BMDLs indicated are doses associated with the 10th percentile value for hemoglobin concentration in normal beagle dogs and are in units of mg/kg/day.
BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: Stebbins et al. 1999

Figure A-10. Linear Model Predicted Change in Hemoglobin Concentration in Female Beagle Dogs Exposed to 1,3-Dichloropropene in the Diet for 1 Year*



*BMDs and BMDLs indicated are doses associated with the 10th percentile value for hemoglobin concentration in normal beagle dogs and are in units of mg/kg/day
BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose

Source: Stebbins et al. 1999

Agency Contacts (Chemical Managers): Annette Ashizawa, Sharon Wilbur, and Heraline Hicks

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not

meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

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

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

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

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

LEGEND

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

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

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

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system,

which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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

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

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

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

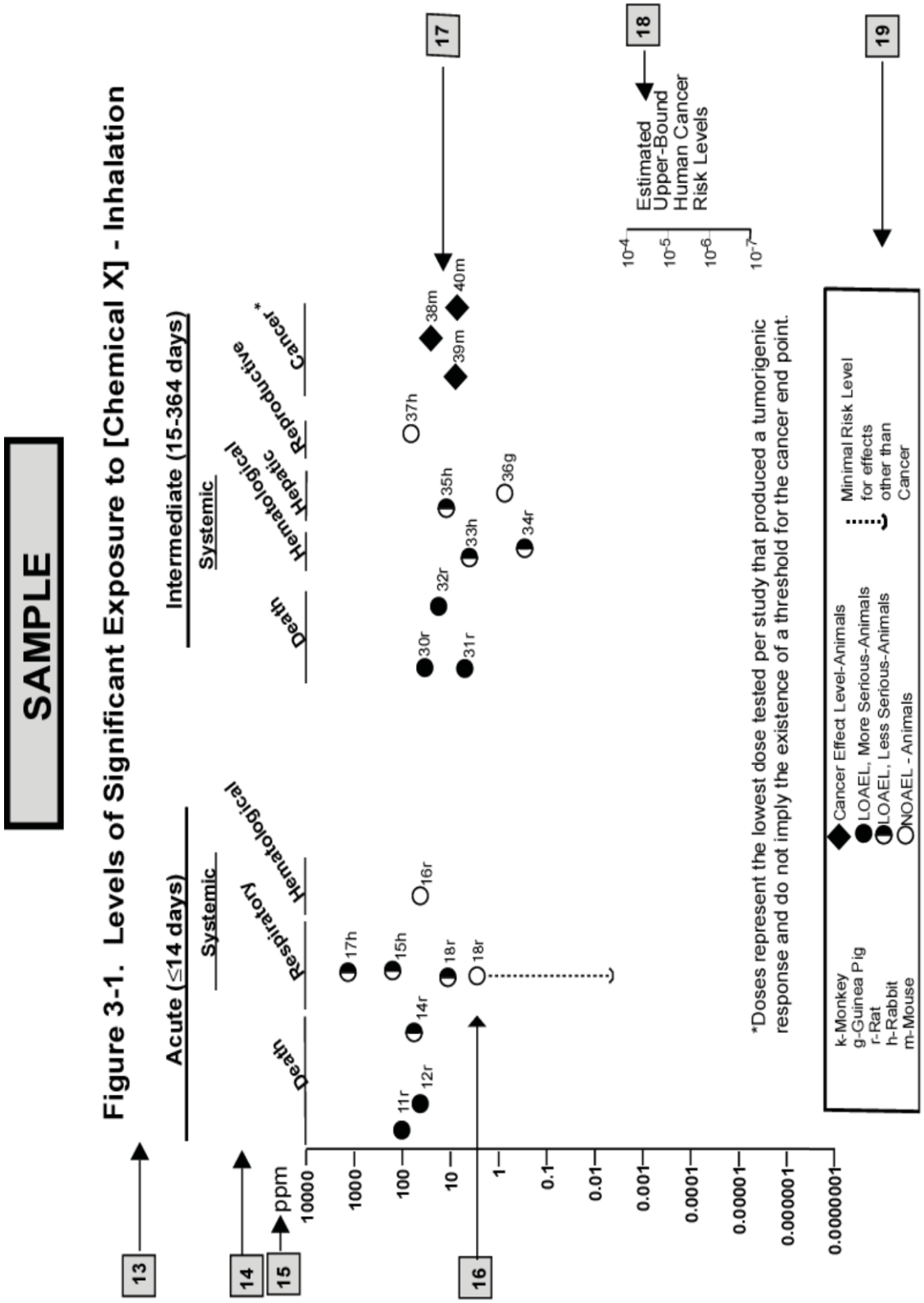
(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **Table 3-1. 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	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).


SAMPLE
Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation
Acute (≤14 days)
Intermediate (15-364 days)
Systemic
Respiratory
Hematological
Death
Hepatic
Reproductive
Cancer *
ppm
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
11r
12r
14r
15h
16r
17h
18r
18r
30r
31r
32r
33h
34r
35h
36g
37h
38m
39m
40m
Estimated Upper-Bound Human Cancer Risk Levels
10^{-4}
10^{-5}
10^{-6}
10^{-7}
*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.
k-Monkey
g-Guinea Pig
r-Rat
h-Rabbit
m-Mouse
Cancer Effect Level-Animals
LOAEL, More Serious-Animals
LOAEL, Less Serious-Animals
NOAEL - Animals
Minimal Risk Level for effects other than Cancer
13
14
15
16
17
18
19

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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

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

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

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

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APPENDIX D. INDEX