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 necessarily mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology 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-62, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: August 2011
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 8
Species: Human

Minimal Risk Level: 2 [ ] mg/kg/day [X] ppm

Reference: Ernstgård L, Iregren A, Sjögren B, et al. 2006. Acute effects of exposure to vapours of dioxane in humans. Human Exp Toxicol 25:723-729.

Experimental design: The acute-duration inhalation MRL is based on a NOAEL of 20 ppm for eye and respiratory effects in volunteers. In that study, six male and six female volunteers were exposed to 0 or 20 ppm 1,4-dioxane vapor for 2 hours under dynamic conditions. Each subject was exposed on two separate occasions to 0 or 20 ppm. End points monitored included self-rated symptoms on a visual analogue scale that measured discomfort of the eyes, nose and throat, breathing difficulty, solvent smell, headache, fatigue, nausea, dizziness and 'feeling of intoxication'. Rating was performed before, during (3, 60, and 118 minutes), and after exposure (20 and 180 minutes). Respiratory function was assessed by spirometry before exposure, immediately after, and 3 hours after exposure ceased. The specific parameters measured included vital capacity, forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow, and forced expiratory flow at 25, 50, and 75% of the force vital capacity. Also assessed was nasal swelling before, immediately after, and 3 hours after exposure. Eye blinking was monitored throughout the exposure period by electromyography. Also, two inflammatory markers, high sensitivity C reactive protein and interleukin 6, were measured in blood before and 3 hours after exposure.

Effects noted in study and corresponding doses: Exposure to 1,4-dioxane under the conditions of the study did not significantly affect any of the end points monitored except the perception of smell of the chemical, which increased significantly after 3, 60, and 118 minutes if exposure. The NOAEL of 20 ppm was divided by an uncertainty factor of 10 (for human variability) to yield the MRL of 2 ppm. An adjustment to 24-hour exposure was not necessary because the first effects observed, as shown by Young et al. (1977), are local irritation effects that are not time-dependent.

Dose and end point used for MRL derivation: 20 ppm; NOAEL for eye and respiratory effects in humans.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

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

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

Other additional studies or pertinent information which lend support to this MRL: Support for the acute-duration inhalation MRL of 2 ppm is provided by a study by Young et al. (1977) in which four healthy male volunteers were exposed to 50 ppm 1,4-dioxane for 6 hours under dynamic airflow conditions. Prior to the study, the subjects provided a complete history and underwent tests including chest x-ray, EKG, respiratory function tests, a conventional battery of 12 blood chemistry tests plus triglyceride and creatinine determinations, and complete hematological and urine analyses. Except for the chest x-ray, the tests were repeated 24 hours and 2 weeks after the exposure. The tests conducted 24 hours and 2 weeks after exposure did not reveal any exposure-related abnormalities, although no data were provided in the study. Eye irritation was a frequent and the only complaint throughout the exposure. Tolerance to the odor of 1,4-dioxane occurred during exposure. Two of the subjects could not perceive the odor after 4 and 5 hours in the chamber. The 50 ppm exposure level constitutes a minimal LOAEL for eye irritation, although there was no control experiment, and possible low humidity in the exposure chamber (not addressed in the report) might have contributed to the eye irritation.

Other studies with volunteers also support the findings of Ernstgård et al. (2006) and Young et al. (1977). For example, Silverman et al. (1946) exposed 12 subject to various concentrations of 1,4-dioxane for only 15 minutes and determined a NOAEL of 200 ppm for eye and nose irritation; the LOAEL was 300 ppm. Wirth and Klimmer (1936) reported that slight mucous membrane irritation started to take place in volunteers at exposure concentrations about 278 ppm for a few minutes (unspecified) and that at 1,390 ppm for several minutes, the subjects described prickling in the nose and scratchiness and dryness in the throat. Fairley et al. (1934) reported a NOAEL of 2,000 ppm (only level tested) for respiratory and ocular effects in six subjects exposed to 1,4-dioxane for only 3 minutes. Finally, Yant et al. (1930) described slight eye, nose, and throat irritation in a group of five subjects exposed to 1,600 ppm (only level tested) 1,4-dioxane for only 10 minutes. The available studies in animals used exposure concentrations that often caused death among the animals and were much higher than the concentrations tested by Young et al. (1977).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: August 2011
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 19
Species: Rat

Minimal Risk Level: 0.2 [ ] mg/kg/day [X] ppm

Reference: Kasai T, Saito M, Senoh H, et al. (2008). Thirteen-week inhalation toxicity of 1,4-dioxane in rats. Inhalation Toxicol 20: 961-971.

Experimental design: Groups of F344 DuCrj rats (10/sex/group) were exposed to target concentrations of 0 (clean air), 100, 200, 400, 800, 1,600, 3,200, or 6,400 ppm 1,4-dioxane vapors 6 hours/day, 5 days/week, for 13 weeks (Kasai et al. 2008). End points evaluated included mortality, clinical signs (daily), body weight and food consumption (once per week), hematology, clinical chemistry and urinalysis at termination, and gross and microscopic pathology of all major organs and tissues.

Effects noted in study and corresponding doses: All rats in the 6,400 ppm group died during the first week of the study. Examination of these rats showed that death was primarily caused by renal failure, as judged by marked necrosis observed in the renal tubules. Lung congestion was also observed in males and females from this exposure group. No abnormal clinical signs were observed during the study. Terminal body weight was reduced in all treated groups except the 100 ppm group, but not in a dose-related manner; the final weight reduced more than 10% relative to controls only in females exposed to 3,200 ppm. Data on food consumption were not provided. Changes in organ weight were limited to the liver, kidneys, and lungs and consisted in increases in relative organ weight generally in the high-dose groups of up to 15% relative to controls; data on absolute organ weights were not provided. Significant changes (although within normal values) in hematology and clinical chemistry parameters were limited to the 3,200 ppm groups and consisted of increases in mean corpuscular volume and serum ALT in males, decreases in glucose and triglycerides in males, and increases in red blood cell count, hemoglobin, hematocrit, and AST and ALT serum activities in females. Histologically, exposure to 1,4-dioxane affected principally the respiratory tract, in particular the nasal cavity of males and females. Significant nuclear enlargement of the respiratory epithelium was seen in all exposed groups. The incidences in males were 0/10 in the control group and 7/10, 9/10, 7/10, 10/10, 10/10, and 10/10 in exposed groups up to 3,200 ppm, respectively. The corresponding incidences in females were 0/10, 5/10, 9/10, 10/10, 10/10, 10/10, and 10/10. Severity of the lesion was dose-related. Significant nuclear enlargement of the olfactory epithelium started at 200 ppm (5/10 in males and 6/10 in females). Similar lesions in the trachea and bronchus appeared only in the high-exposure groups. The nuclear enlargement was characterized by the epithelial cells having a round to oval or elongated nucleus at least 4 times larger in diameter than normal. Significantly increased incidence of vacuolic change started in males at 400 ppm (0/10, 1/10, 3/10, 6/10, 10/10, 9/10) and in females at 800 ppm (0/10, 1/10, 2/10, 3/10, 7/10, 9/10, 10/10), while atrophy of the olfactory epithelium started in females at 800 ppm (0/10, 0/10, 2/10, 3/10, 5/10, 5/10, 4/10); incidence of atrophy of the olfactory epithelium in males was not presented. Significant single cell necrosis and centrilobular swelling occurred in the liver of males exposed to 3,200 ppm 1,4-dioxane; females in this exposure group showed only centrilobular swelling. Significant kidney changes were seen only in females from the 3,200 ppm exposure group and consisted of hydropic changes in the proximal tubule. No treatment-related lesions were reported in any other tissue or organ examined. Although

nuclear enlargement of the respiratory and olfactory epithelium occurred at lower exposure levels than other nasal lesions, it was not selected as the critical effect for MRL derivation on the grounds that the toxicological significance of the lesion is uncertain. There is some evidence suggesting that this alteration may represent a preneoplastic lesion. As discussed by Kasai et al. (2008), nuclear enlargement occurred as an early histopathological change in the respiratory tract of rats simultaneously exposed to sulfur dioxide and treated intraperitoneally with several N-nitrosamines known to induce nasal tumors in rats (Fowlie et al. 1990). In addition, studies have shown a good correlation between *in vivo* carcinogenicity and the extent of nuclear enlargement in HeLa cells *in vitro* (Grant and Grasso 1978). Since MRLs are not based on a consideration of cancer effects, nuclear enlargement is not considered a suitable basis of an MRL.

Dose and end point used for MRL derivation: $BMCL_{10}$ of 27.99 ppm for lesions in the olfactory epithelium of the nasal cavity in male rats.

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

Uncertainty Factors used in MRL derivation:

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

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

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: The intermediate-duration inhalation MRL was calculated using EPA's methodology (EPA 1994) for a category 3 gas, as explained in detail in Section 2.3 (derivation of the intermediate-duration inhalation MRL). A duration adjustment (6/24 hours x 5/7 days) seemed appropriate in the absence of information regarding whether Haber's Law is applicable under the experimental conditions of the study.

The MRL is derived as follows:

$$BMCL_{10[HEC]} = BMCL_{10[ADJ]} \times (H_{b/g}A / H_{b/g}H)$$

where:
$BMCL_{10[ADJ]}$ = 27.99 ppm x 6/24 hours x 5/7 days = 4.998 ppm and
$H_{b/g}A$ = animal blood:air partition coefficient = 1,861 (Sweeney et al. 2008)
$H_{b/g}H$ = human blood:air partition coefficient = 1,666 (Sweeney et al. 2008)

$$(H_{b/g}A / H_{b/g}H) = 1{,}861/1{,}666 = 1.117$$

Because the ratio of the partition coefficients is higher than 1, a default value of 1 is used in accordance with EPA's RfC methodology (EPA 1994).

$$BMCL_{[HEC]} = 4.998 \text{ ppm} \times 1 = 4.998 \text{ ppm}$$

Other additional studies or pertinent information which lend support to this MRL: Only one additional intermediate-duration inhalation study that exposed several animal species to high concentrations of 1,4-dioxane and monitored limited end points is available (Fairley et al. 1934). In that study, rats, mice,

guinea pigs, and rabbits were exposed to airborne 1,4-dioxane 3 hours/day, 5 days/week for periods of up to 12 weeks. At termination, examination of the animals revealed moderate to severe liver and kidney toxicity occurring at all exposure levels in all of the species tested. The lowest exposure level was 1,000 ppm. In a 2-year inhalation study, nasal alterations in both the respiratory and olfactory epithelium were reported in male rats (females were not tested) exposed to ≥50 ppm 1,4-dioxane vapors 6 hours/day, 5 days/week (Kasai et al. 2009). In the chronic-duration inhalation study in rats conducted by Torkelson et al. (1974), no interim histopathological evaluations were performed. In that study, rats were exposed 111 ppm 1,4-dioxane 7 hours/day (1 hour longer than Kasai et al. [2008]), 5 days/week for 2 years. Although Torkelson et al. (1974) reported that there were no treatment-related gross or microscopic lesions in the tissues examined and explicitly mention that there were no nasal tumors, the nasal cavity was not listed among the tissues and organs that were subjected to microscopic examination.

Agency Contact (Chemical Manager): Sharon Wilbur

BENCHMARK MODELING FOR CHANGES IN THE OLFACTORY EPITHELIUM IN RATS

Incidence data (Table A-1) for vacuolic change in the olfactory epithelium in male and female rats and of atrophy of the olfactory epithelium in female rats exposed to 1,4-dioxane vapors (Kasai et al. 2008) were analyzed using the BMD/BMC approach for MRL derivation. Models in the EPA Benchmark Dose Software (BMDS version 2.1.1) (Gamma, Logistic, Log-logistic, Multi-stage, Probit, Log-probit, Weibull models) were fit to the nasal lesions data to determine potential points of departure for the MRL. Adequate model fit is judged by three criteria: goodness-of-fit ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest benchmark concentration (BMCL, the lower limit of a one-sided 95% confidence interval on the BMC) is selected as the point of departure when differences between the BMCLs estimated from these models are more than 3-fold; otherwise, the BMCL from the model with the lowest Akaike's information criterion (AIC) is chosen. In accordance with EPA (2000a) guidance, BMCs and BMCLs associated with an extra risk of 10% are calculated for all models. Attempts to model the incidence of vacuolic change in the olfactory epithelium from male rats were unsuccessful in that none of the models could fit the data and/or had overall largest scaled residuals that exceeded the maximum value criteria of 2 (Table A-2). However, all models provided adequate fits after the highest dose was dropped. The best fit was provided by a Multistage (1-degree) model with a lowest predicted exposure concentrations associated with a 10% extra risk (BMC_{10}) of 40.39 ppm and a corresponding lower 95% confidence limit on this concentration ($BMCL_{10}$) of 27.99 ppm. Graphic representation of the fit is presented in Figure A-1. The best fit for the incidence data for vacuolic change in the olfactory epithelium from female rats was provided also by a Multistage (1-degree) model; the BMC_{10} and $BMCL_{10}$ values were 80.30 and 56.78 ppm, respectively (Table A-3); the dose-response curve is shown in Figure A-2. The best fit for the incidence data for atrophy of the olfactory epithelium in female rats was provided by a LogLogistic model; the BMC_{10} and $BMCL_{10}$ values were 172.57 and 103.81 ppm, respectively (Table A-4); the graphic representation of the fit is shown in Figure A-3. In order to be protective of human health, the lowest $BMCL_{10}$ of 27.99 ppm from the incidence of vacuolic change in the olfactory epithelium of male rats is selected as point of departure for MRL derivation. The $BMCL_{10}$ of 27.99 ppm was converted to a HEC ($BMCL_{10[HEC]}$) using the EPA cross-species dosimetric methodology (EPA 1994) for a category 3 gas, as explained in detail in Section 2.3.

Table A-1. Incidence Data for Vacuolic Change and Atrophy in the Nasal Cavity Olfactory Epithelium in F344 Rats Exposed to 1,4-Dioxane

Exposure concentration (ppm)						
0	100	200	400	800	1,600	3,200
Male rats (vacuolic change)						
0/10	1/10	3/10	6/10	10/10	10/10	9/10
Female rats (vacuolic change)						
0/10	1/10	2/10	3/10	7/10	9/10	10/10
Female rats (atrophy)						
0/10	0/10	2/10	3/10	5/10	5/10	4/10

Source: Kasai et al. 2008

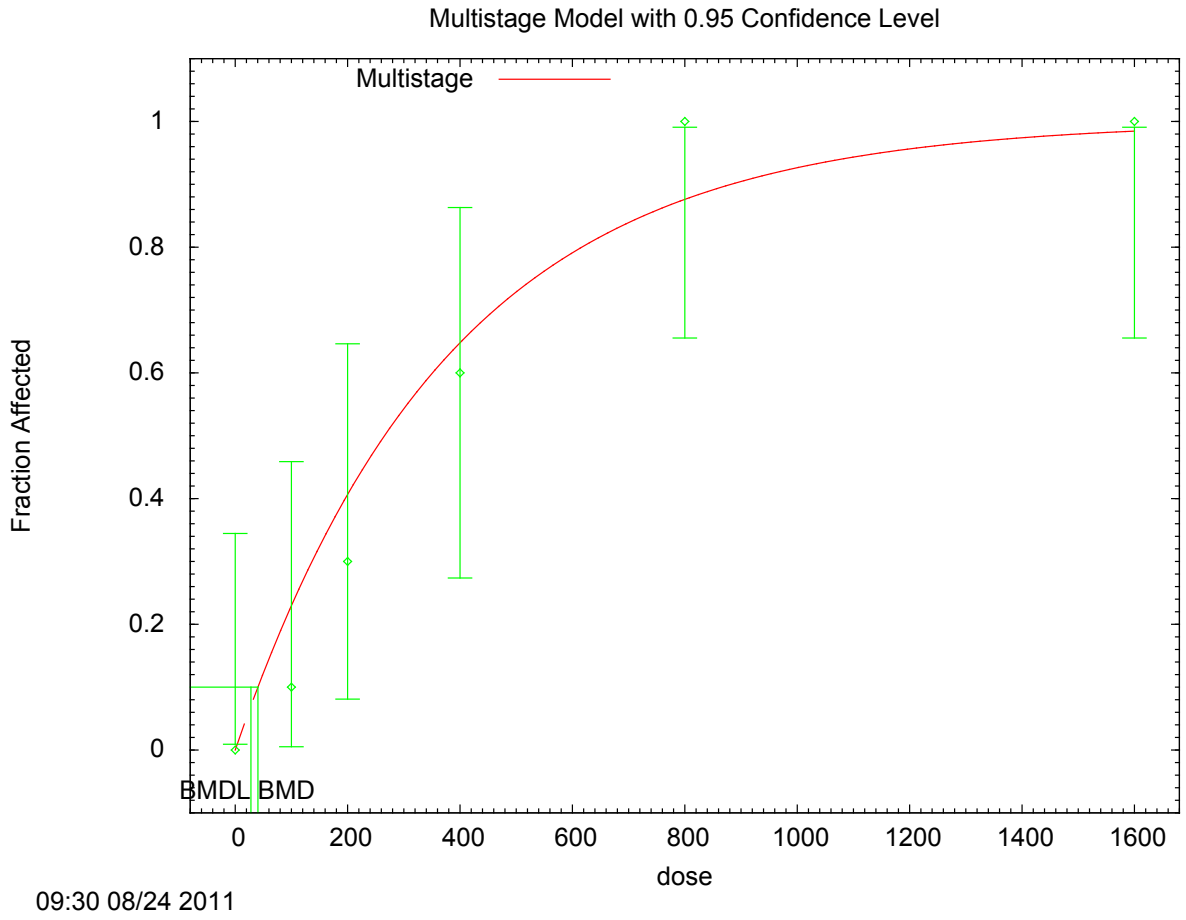
Table A-2. Model Predictions for the Incidence of Vacuolic Change in the Olfactory Epithelium In Male Rats Exposed to 1,4-Dioxane

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
All doses									
Gamma[c]	6	43.56	0	0.00	-0.60	-6.30	52.92	ND	ND
Logistic	5	316.7	0	-1.10	-0.07	-17.55	66.26	ND	ND
LogLogistic[d]	5	9.35	0.10	0.00	-0.15	-2.70	49.16	ND (LS)	ND (LS)
LogProbit[d]	6	11.88	0.06	0.00	-0.33	-3.04	48.51	ND	ND
Multistage (1-degree)[e]	6	43.56	0	0.00	-0.60	-6.30	52.92	ND	ND
Multistage (2-degree)[e]	6	43.56	0	0.00	-0.60	-6.30	52.92	ND	ND
Multistage (3-degree)[e]	6	43.56	0	0.00	-0.60	-6.30	52.92	ND	ND
Multistage (4-degree)[e]	6	43.56	0	0.00	-0.60	-6.30	52.92	ND	ND
Multistage (5-degree)[e]	6	43.56	0	0.00	-0.60	-6.30	52.92	ND	ND
Multistage (6-degree)[e]	6	43.56	0	0.00	-0.60	-6.30	52.92	ND	ND
Probit	5	56.22	0	-1.42	-0.30	-6.40	71.55	ND	ND
Weibull[c]	6	43.56	0	0.00	-0.60	-6.30	52.92	ND	ND
Highest dose dropped									
Gamma[c]	4	0.79	0.94	0.25	0.09	-0.61	37.29	112.53	47.46
Logistic	4	1.09	0.90	0.07	0.65	0.65	37.70	140.81	91.82
LogLogistic[d]	4	1.65	0.80	0.48	0.06	-0.82	38.47	121.09	64.79
LogProbit[d]	4	1.48	0.83	0.50	-0.09	-0.78	38.16	118.46	66.52
Multistage (1-degree)[e,f]	***5***	***3.09***	***0.69***	***0.00***	***-0.98***	***1.19***	***38.86***	***40.39***	***27.99***
Multistage (2-degree)[e]	4	0.42	0.98	0.05	0.20	-0.45	36.76	103.17	42.53
Multistage (3-degree)[e]	4	0.22	0.99	0.00	-0.16	0.30	36.45	86.98	39.84
Multistage (4-degree)[e]	3	0.16	0.98	0.00	-0.22	0.28	38.35	82.28	37.99
Multistage (5-degree)[e]	3	0.12	0.99	0.00	-0.19	0.25	38.30	84.93	37.02
Probit	4	0.79	0.94	0.09	0.57	0.57	37.26	131.72	86.59
Weibull[c]	4	0.52	0.97	0.19	0.23	-0.51	36.87	111.01	49.07

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-1. Fit of Multistage 1 Degree Polynomial Model to Data on 1,4-Dioxane, Incidence of Vacuolic Change in the Olfactory Epithelium of Male Rats Exposed via Inhalation for 13 Weeks



Source: Kasai et al. 2008

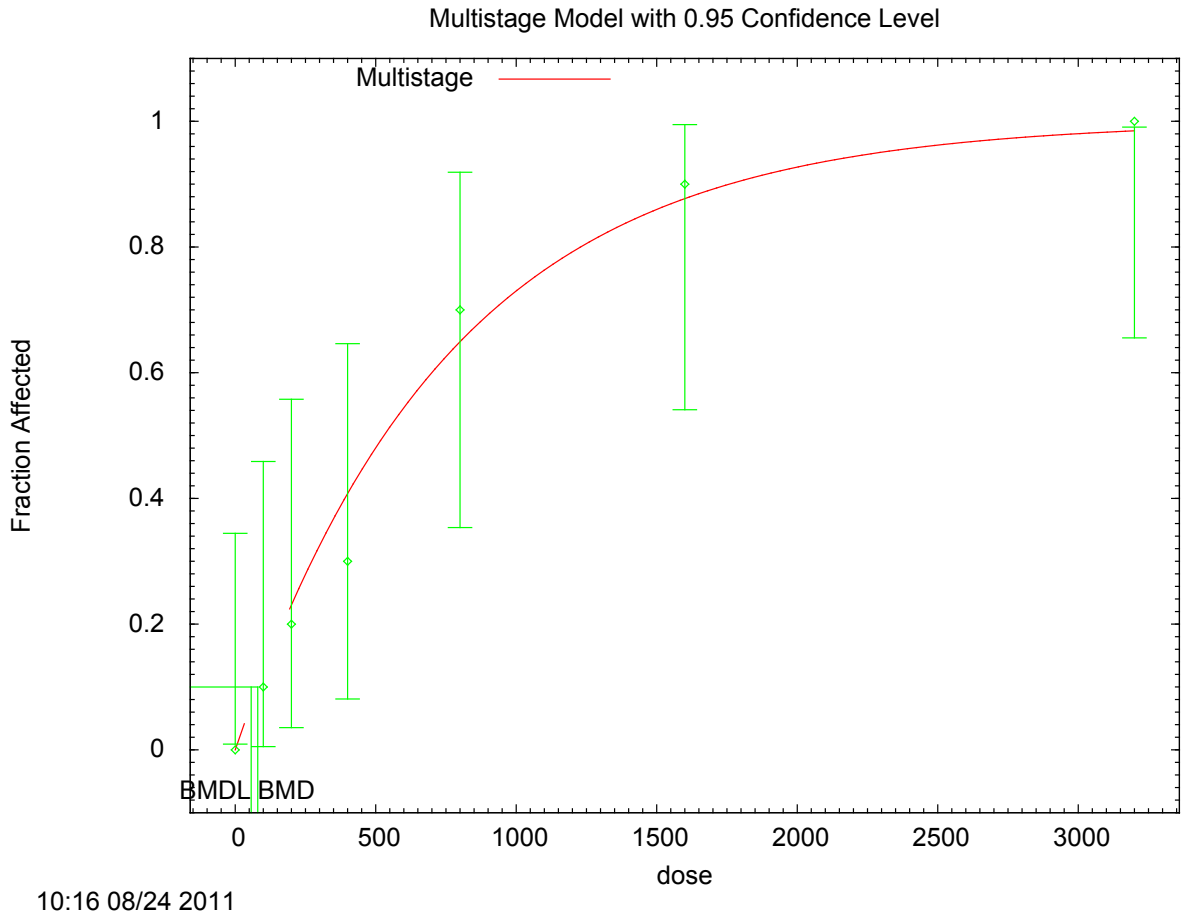
Table A-3. Model Predictions for the Incidence of Vacuolic Change in the Olfactory Epithelium in Female Rats Exposed by Inhalation to 1,4-Dioxane Vapor for 13 Weeks

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b]: Dose below BMC	Scaled residuals[b]: Dose above BMC	Scaled residuals[b]: Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[c]	5	0.46	0.99	0.22	0.14	-0.51	51.97	119.11	58.89
Logistic	5	2.48	0.78	0.35	0.18	-0.97	54.53	238.59	165.80
LogLogistic[d]	5	1.30	0.93	0.59	0.25	-0.75	53.05	141.58	64.86
LogProbit[d]	5	1.35	0.93	0.64	0.12	-0.81	53.00	136.97	95.47
Multistage (1-degree)[e,f]	***6***	***0.90***	***0.99***	***0.00***	***-0.22***	***0.39***	***50.52***	***80.30***	***56.78***
Multistage (2-degree)[e]	5	0.39	1.00	0.04	0.09	-0.41	51.86	104.27	59.36
Multistage (3-degree)[e]	5	0.39	1.00	0.04	0.09	-0.41	51.86	104.27	59.36
Multistage (4-degree)[e]	4	0.40	0.98	0.04	0.09	0.42	53.86	103.74	59.36
Multistage (5-degree)[e]	4	0.39	0.98	0.03	0.08	0.43	53.85	103.04	59.32
Multistage (6-degree)[e]	4	0.39	0.98	0.03	0.08	0.43	53.85	102.80	59.27
Probit	5	2.59	0.76	0.33	0.19	-0.96	54.71	230.67	165.00
Weibull[c]	5	0.42	0.99	0.19	0.14	-0.47	51.90	116.72	59.17

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom

Figure A-2. Fit of Multistage 1 Degree Polynomial Model to Data on 1,4-Dioxane, Incidence of Vacuolic Change in the Olfactory Epithelium of Female Rats Exposed via Inhalation for 13 Weeks



Source: Kasai et al. 2008

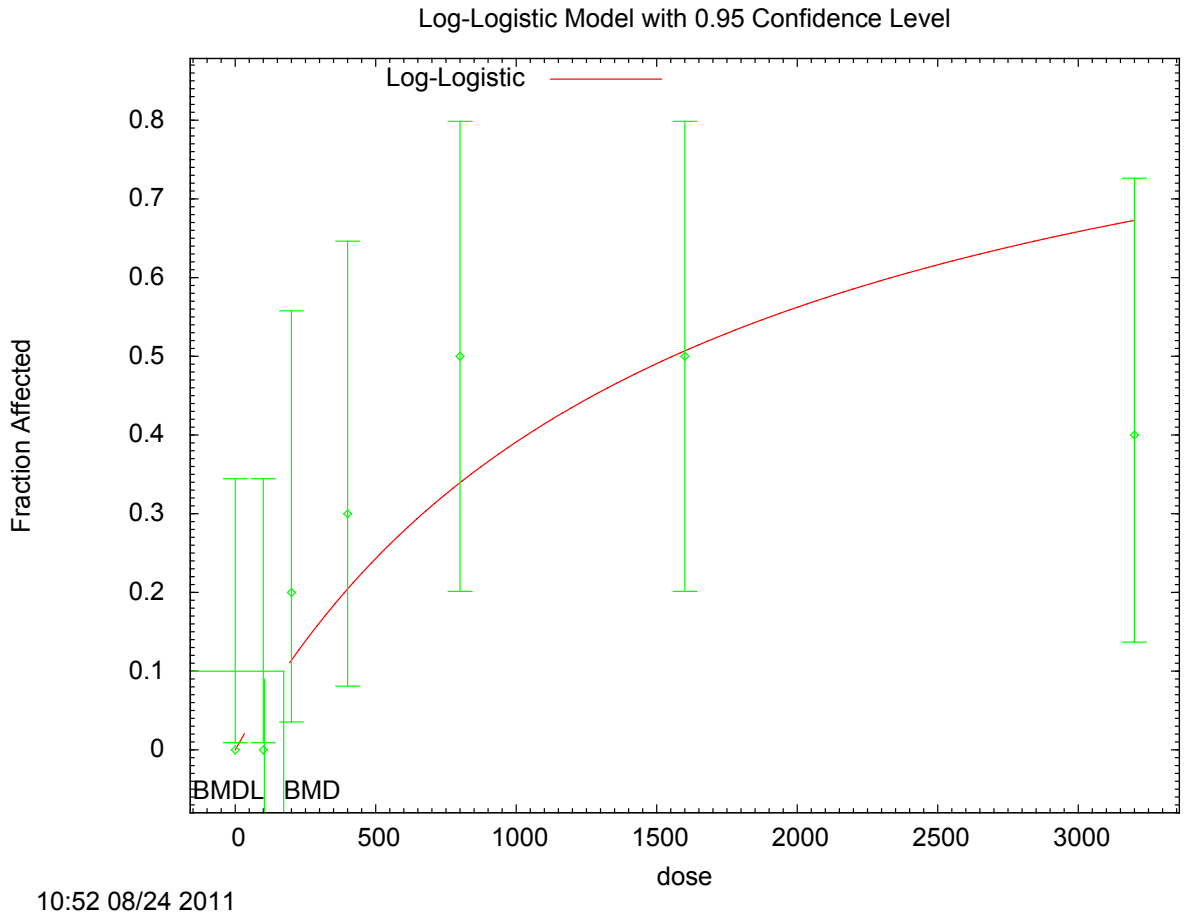
Table A-4. Model Predictions for the Incidence of Atrophy of the Olfactory Epithelium in Female Rats Exposed by Inhalation to 1,4-Dioxane Vapor for 13 Weeks

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Scaled residuals[b] Dose above BMC	Scaled residuals[b] Overall largest	AIC	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Gamma[c]	5	9.15	0.10	0.77	1.05	-1.71	77.39	336.54	193.55
Logistic	5	10.35	0.07	1.84	1.08	1.84	80.74	898.33	580.22
LogLogistic[d,e]	***6***	***6.47***	***0.37***	***-0.80***	***0.86***	***-1.84***	***71.99***	***172.57***	***103.81***
LogProbit[d]	5	11.48	0.04	1.17	1.78	-1.87	80.50	ND	ND
Multistage (1-degree)[f]	5	9.15	0.10	0.77	1.05	-1.71	77.39	336.54	193.55
Multistage (2-degree)[f]	5	9.15	0.10	0.77	1.05	-1.71	77.39	336.54	193.55
Multistage (3-degree)[f]	5	9.15	0.10	0.77	1.05	-1.71	77.39	336.54	193.55
Multistage (4-degree)[f]	5	9.15	0.10	0.77	1.05	-1.71	77.39	336.54	193.55
Multistage (5-degree)[f]	5	9.15	0.10	0.77	1.05	-1.71	77.39	336.54	193.55
Multistage (6-degree)[f]	5	9.15	0.10	0.77	1.05	-1.71	77.39	336.54	193.55
Probit	5	10.26	0.07	1.85	1.06	-1.48	80.52	846.81	557.27
Weibull[c]	5	9.15	0.10	0.77	1.05	-1.71	77.39	336.54	193.55

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

Figure A-3. Fit of Log Logistic Model to Data on 1,4-Dioxane, Incidence of Atrophy of the Olfactory Epithelium in Female Rats Exposed via Inhalation for 13 Weeks



Source: Kasai et al. 2008

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: August 2011
Profile Status: Final
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 27
Species: Rat

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

Reference: Kasai T, Kano H, Umeda Y, et al. 2009. Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male. Inhal Toxicol 21:889-897.

Experimental design: Groups of male F344/DuCrj rats (50/group) were exposed whole-body to target concentrations of 0, 50, 250, or 1,250 ppm 1,4-dioxane vapors 6 hours/day, 5 days/week for 104 weeks; controls were exposed to clean air. End points evaluated included clinical signs and mortality (daily) and body weight and food consumption (once /week for the first 14 weeks, every 4 weeks thereafter). All rats were subjected to complete necropsy. Blood was collected at termination for clinical chemistry and hematology tests; urinary pH was measured in the last week of the study. All major organs were removed, weighed, and examined for macroscopic lesions. All major tissues and organs, including the entire respiratory tract, were examined microscopically.

Effects noted in study and corresponding doses: Survival rates in rats exposed to 250 ppm tended to decrease relative to controls, but the difference with controls was not statistically significant. Exposure to 1,250 ppm 1,4-dioxane significantly reduced ($p<0.05$) survival rate beginning on week 91. Terminal survival rate was 37/50, 37/50, 29/50, and 25/50 in the control, low-, mid-, and high-exposure groups, respectively. The decreased survival rates were attributed to increased number of deaths due primarily to peritoneal mesotheliomas, although nasal tumors contributed to the causes of death. Terminal body weight was reduced 6.3% in the high-exposure group. Food consumption was not affected by exposure to 1,4-dioxane. Significant increases in relative liver (27%) and lung (2%) weights were reported in the high-exposure group but there was no clear dose-response relationship. Significant changes in hematology and clinical chemistry tests included reduced hemoglobin (13%), MCV (6%), MCH (8%), increased serum AST (46%), ALT (95%), AP (15%), and γ-GTP (6–7-fold); urinary pH was reduced 7%. All of these changes were restricted to the high-exposure group. Treatment-related pre- and nonneoplastic lesions occurred in the nasal cavity, liver, and kidney. All exposed groups had significant increases in nuclear enlargement of the respiratory epithelium (0/50, 50/50, 48/50, 38/50), nuclear enlargement of the olfactory epithelium (0/50, 48/50, 48/50, 45/50), atrophy of olfactory epithelium (0/50, 40/50, 47/50, 48/50), and respiratory metaplasia of the olfactory epithelium (11/50, 34/50, 49/50, 48/50). Significant increases in liver lesions (centrilobular nuclear enlargement, acidophilic cell foci, basophilic cell foci, spongiosis hepatis, and centrilobular necrosis) occurred in the high-exposure group. Significant increases in nuclear enlargement of the proximal kidney tubule occurred in the mid- and high-exposure groups; significantly increased incidence of hydropic changes in the proximal tubule occurred in the high-exposure group. No significant changes occurred in other organs or tissues. The lowest exposure concentration tested, 50 ppm 1,4-dioxane, is a LOAEL for nasal lesions (atrophy of the olfactory epithelium), a NOAEL was not defined in this study.

The results of Kasai et al. (2009) clearly show that the nasal cavity was the most sensitive tissue following 2 years of exposure to 1,4-dioxane vapors. As discussed in the derivation of the intermediate-duration inhalation MRL for 1,4-dioxane, nuclear enlargement will not be considered a suitable basis for derivation of an MRL because it may represent a pre-neoplastic lesion. Incidences of atrophy (0/50, 40/50, 47/50, and 48/50) and respiratory metaplasia (11/50, 34/50, 49/50, and 48/50) of the olfactory epithelium were also significantly elevated at all exposure levels tested. Of these two lesions, the atrophy of the olfactory epithelium was selected as the critical effect for MRL derivation because it showed a higher incidence rate at the LOAEL than respiratory metaplasia. Because the incidence of this lesion at the lowest exposure level (50 ppm) was close to the maximal response level (80% of 50-ppm animals showed this lesion), BMD analysis of the data was not conducted. This decision is in accordance with guidelines stating that studies in which responses are at or near the maximal response level are not considered adequate for BMD analysis (EPA 2000a).

Dose and end point used for MRL derivation: 50 ppm; LOAEL for atrophy of the olfactory epithelium of the nasal cavity in male rats.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

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

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose: The chronic-duration inhalation MRL was calculated using EPA's methodology (EPA 1994) for a category 3 gas, as explained in detail in Section 2.3 (derivation of the intermediate-duration inhalation MRL). A duration adjustment (6/24 hours x 5/7 days) seemed appropriate in the absence of information regarding whether Haber's Law is applicable under the experimental conditions of the study.

The MRL is derived as follows:

$$LOAEL_{[HEC]} = LOAEL_{[ADJ]} \times (H_{b/g}A / H_{b/g}H)$$

where:
$LOAEL_{[ADJ]}$ = 50 ppm x 6/24 hours x 5/7 days = 8.9286 ppm and
$H_{b/g}A$ = animal blood:air partition coefficient = 1,861 (Sweeney et al. 2008)
$H_{b/g}H$ = human blood:air partition coefficient = 1,666 (Sweeney et al. 2008)

$$(H_{b/g}A / H_{b/g}H) = 1{,}861/1{,}666 = 1.117$$

Because the ratio of the partition coefficients is higher than 1, a default value of 1 is used in accordance with EPA's RfC methodology (EPA 1994).

$$LOAEL_{[HEC]} = 8.9286 \text{ ppm} \times 1 = 8.9286 \text{ ppm}$$

Other additional studies or pertinent information which lend support to this MRL: In a study conducted by Torkelson et al. (1974), groups of Wistar rats (288/sex) were exposed to 1,4-dioxane vapors at a

concentration of 0.4 mg/L (111 ppm) 7 hours/day, 5 days/week for 2 years. Controls were exposed to filtered room air. End points examined included clinical signs, eye and nasal irritation, skin condition, respiratory distress, and tumor formation. Hematological parameters (hemoglobin, red blood cell count, total and differential leukocyte counts, corpuscular volume) were determined after 16 and 23 months of exposure. Blood collected at termination was used also for determination of clinical chemistry parameters (serum ALT and alkaline phosphatase activity, BUN, total protein). Liver, kidneys, and spleen were weighed and the major tissues and organs were processed for microscopic examination. Exposure to 1,4-dioxane vapors had no significant effect on mortality or body weight gain and induced no signs of eye or nasal irritation or respiratory distress. Slight but statistically significant changes in hematological and clinical chemistry parameters were within the normal physiological limits and were considered of no toxicological importance. Organ weights were not significantly affected. Microscopic examination of organs and tissues did not reveal treatment-related effects. It should be noted, however, that the tissues from the nasal cavity were not listed among the tissues that were subjected to microscopic examination by Torkelson et al. (1974); therefore, the possibility exists that nasal lesions were present but were not detected. This possibility is strengthened by the results of Kasai et al. (2008) that reported a significant incidence of nasal lesions in rats following inhalation exposure to 100 ppm 1,4-dioxane for 13 weeks.

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: August 2011
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 18
Species: Rat

Minimal Risk Level: 5 [X] mg/kg/day [ ] ppm

Reference: Giavini E, Vismara C, Broccia MA. 1985. Teratogenesis study of dioxane in rats. Toxicol Letters 26:85-88.

Experimental design: Groups of 17–20 pregnant Sprague-Dawley rats were treated with 0, 0.25, 0.5, or 1 mL 1,4-dioxane/kg/day (0, 258, 516, or 1,033 mg 1,4-dioxane/kg/day based on a specific gravity of 1.034) by gavage in water on Gds 6–15. Food consumption was determined daily and body weight was monitored every 3 days. Sacrifices were conducted on Gd 21 and the number of corpora lutea, implantations, resorptions, and liver fetuses was recorded. The fetuses were weighed and inspected for external malformations and half were examined for visceral abnormalities; the other half were examined for skeletal malformations.

Effects noted in study and corresponding doses: Rats treated with 1,033 mg 1,4-dioxane/kg/day gained 18% less weight than controls during treatment days, although the difference was not statistically significant. Food consumption was slightly (5%) but significantly ($p<0.05$) reduced in these rats during treatment. The average fetal weight in the high-dose group was slightly but significantly ($p<0.01$) lower than in controls. Also, a slight but significant ($p<0.05$) reduction in sternum ossification was seen in high-dose fetuses. There were no significant effects on the number of implantations and live fetuses, post-implantation loss, or incidence of malformations. Based on the reduced maternal and fetal body weight and reduced sternum ossification, a maternal and developmental LOAEL of 1,013 mg 1,4-dioxane/kg/day can be defined; the maternal and developmental NOAEL is 516 mg/kg/day. Attempts made to apply dose-response models to the data were unsuccessful, as no adequate fits of EPA BMDS models to the data were obtained; therefore, the NOAEL/LOAEL approach was used for MRL derivation.

Dose and end point used for MRL derivation: 516 mg/kg/day; NOAEL for developmental and maternal effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion used from ppm in food or water to a mg/body weight dose? A conversion was done from mL of 1,4-dioxane to mg of 1,4-dioxane using the specific gravity of 1,4-dioxane.

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

Other additional studies or pertinent information which lend support to this MRL: JRBC (1998) conducted a 2-week drinking water study in F344 rats and B6C3F$_1$ mice and reported that the most sensitive effect was an increased incidence of nuclear enlargement of the olfactory epithelium in male and female rats receiving doses of approximately 1,010 and 1,040 mg 1,4-dioxane/kg/day, respectively; the corresponding NOAELs were 370 and 400 mg/kg/day. The use of the nasal lesions as the point of departure for MRL derivation was precluded by recent data strongly suggesting that these lesions in rats are due to direct contact of the drinking water containing 1,4-dioxane with nasal epithelium while the rats drink the water(Sweeney et al. 2008). Increased incidence of hepatocyte swelling and vacuolation and hydropic changes in the renal proximal tubule were also reported in male and female rats dosed with 2,960 and 2,750 mg 1,4-dioxane/kg/day, respectively; the corresponding NOAELs were 1,010 and 1,040 mg/kg/day. Although the NOAELs for liver and kidney changes could have been considered as points of departure for MRL derivation, several study limitations, including the lack of statistical analysis of the results due to the fact that only 2 or 3 animals (out of 10/group) were examined, and the fact that end points such as hematology, clinical chemistry, clinical signs, and gross examinations were not conducted or reported, severely compromise the interpretation of the results.

Agency Contact (Chemical Manager): Sharon Wilbur

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: August 2011
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 22
Species: Rat

Minimal Risk Level: 0.5 [X] mg/kg/day [ ] ppm

Reference: Kano et al. 2008. Thirteen-week oral toxicity of 1,4-dioxane in rats and mice. J Toxicol Sci 33:141-153.

Experimental design: The intermediate-duration oral MRL is based on a NOAEL of 52 mg 1,4-dioxane/ kg/day for liver effects in rats. Groups of F344/DuCrj rats (10/sex/group) were administered 1,4-dioxane in the drinking water in concentrations of 0, 640, 1,600, 4,000, 10,000, or 25,000 ppm for 13 weeks (0, 52, 126, 274, 657, or 1,554 mg/kg/day in males; 0, 83, 185, 427, 756, or 1,614 mg/kg/day in females, estimated by the investigators). End points evaluated included clinical signs (daily), food (once a week) and water consumption (daily), body weight (once a week), complete hematology and clinical chemistry tests (at termination), urinalysis (at termination), organ weights, gross necropsy and histopathology.

Effects noted in study and corresponding doses: One female in the 1,614 mg/kg/day group died. Body weight gain was reduced at 756 mg/kg/day (12%) and 1,614 mg/kg/day (21%) in females and at 1,554 mg/kg/day (21%) in males. Food consumption was reduced 13% in females at 1,614 mg/kg/day. Water consumption was reduced in a dose-related manner in all male groups and in females at ≥126 mg/kg/day. Hematology tests showed significant increases in erythrocyte counts, hemoglobin, hematocrit, and neutrophils, and a decrease in lymphocytes in males at 1,554 mg/kg/day, and decreases in mean corpuscular volume and platelets in females at 1,614 mg/kg/day. Total protein and albumin were decreased in males at ≥274 mg/kg/day and in females at ≥427 mg/kg/day. Serum AST, ALT, AP, and LAP activities, and levels of cholesterol, triglycerides, sodium, and glucose were significantly elevated in high dose males and females. Urinary pH was decreased in males at ≥274 mg/kg/day and in females at ≥756 mg/kg/day. Absolute and relative kidney weights were increased in females at ≥231 mg/kg/day. Nuclear enlargement of the respiratory epithelium occurred in males at ≥126 mg/kg/day and in females at ≥185 mg/kg/day; nuclear enlargement of the olfactory and tracheal epithelium occurred in males at ≥274 mg/kg/day and in females at ≥427 mg/kg/day. Swelling of the central area of the liver was observed in males at ≥126 mg/kg/day and in females at ≥756 mg/kg/day, and vacuolar changes in the liver occurred in males at ≥657 mg/kg/day and in females at 1,614 mg/kg/day. The incidences of swelling of the central area of the liver in males were 0/10, 0/10, 9/10, 10/10, 10/10, and 10/10 in the control, 52, 126, 274, 657, and 1,554 mg/kg/day dose groups, respectively. Nuclear enlargement of the proximal tubule of the kidneys was seen in males at ≥657 mg/kg/day and in females at ≥756 mg/kg/day. Hydropic changes in the proximal tubule of the kidneys and vacuolar changes in the brain occurred in high-dose males and females (1,554 and 1,614 mg/kg/day, respectively). The study LOAEL was 126 mg/kg/day for liver effects in male rats. Limitations of the study include the lack of reporting on clinical signs and gross necropsy. To derive the MRL, the NOAEL of 52 mg/kg/day for liver effects in males was divided by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability), yielding an intermediate-duration oral MRL of 0.5 mg/kg/day. The steepness of the dose-response relationship for liver lesions rendered the data set inadequate for BMD analysis.

Dose and end point used for MRL derivation: 52 mg/kg/day; NOAEL for liver effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion used from ppm in food or water to a mg/body weight dose? The conversion was done by the investigators, and the doses listed are means of ranges provided by the investigators.

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

Other additional studies or pertinent information which lend support to this MRL: A study by Lundberg et al. 1987) supports the liver findings of Kano et al. (2008). The study used male Sprague-Dawley rats (8–11/group) that were treated with 100 or 1,000 mg 1,4-dioxane/kg by gavage in saline 5 days/week for 7 weeks. One week after the last treatment, the rats were killed and the livers were processed for microscopic examination. The livers of high-dose rats showed enlarged foamy hepatocytes mainly in midzonal regions. The foamy appearance was due to vacuoles shown to contain fat. No treatment-related histopathological alterations were observed in the liver at the 100 mg/kg/day dose level. Also supporting the findings from Kano et al. (2008) is a report by Stott et al. (1981) who found that repeated dosing of rats with 1,000 mg 1,4-dioxane/kg/day for 7 or 11 weeks produced hepatocyte swelling and histopathology. Similar findings were reported in an earlier study in which rats were treated with doses of approximately 1,428 mg 1,4-dioxane/kg/day in the drinking water for 34 days (Fairley et al. 1934).

Agency Contact (Chemical Manager): Sharon Wilbur

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,4-Dioxane
CAS Number: 123-91-1
Date: August 2011
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 39
Species: Rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: Kociba RJ, McCollister SB, Park C, et al. 1974. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. Toxicol Appl Pharmacol 30:275-286.

Experimental design: Groups of Sherman rats (60/sex/dose level) were treated with 1,4-dioxane in the drinking water at levels of 0 (controls), 0.01, 0.1, or 1% for 716 days. Based on body weight and water consumption data, the investigators estimated that the water provided doses of 1,4-dioxane of 0, 9.6, 94, and 1,015 mg/kg/day for males and 0, 19, 148, and 1,599 mg/kg/day for females. Blood samples were collected from controls and high-dose rats during the 4th, 6th, 12th, and 18th months of the study and at termination. Additional end points evaluated included clinical signs, body weight, organ weights, and gross and microscopic examination of major tissues and organs.

Effects noted in study and corresponding doses: Treatment with 1,4-dioxane significantly increased mortality in high-dose males and females beginning at about 2–4 months of treatment. These rats showed degenerative changes in both the liver and kidneys. Body weight gain was significantly reduced in high-dose animals from the beginning of the study. Microscopic lesions were restricted to the liver and kidneys from the mid- and high-dose groups. The liver lesions consisted of various degrees of hepatocellular degeneration and necrosis and evidence of hepatic regeneration as indicated by hepatocellular hyperplastic nodule formation. The NOAEL for liver effects was 9.6 mg/kg/day in males and 19 mg/kg/day in females. The LOAELs were 94 mg/kg/day in males and 148 mg/kg/day in females. The kidneys showed tubular epithelial degeneration and necrosis, and there was evidence of renal tubular regeneration as indicated by increased tubular epithelial regenerative activity (≥94 mg/kg/day in males and ≥148 mg/kg/day in females). There were no compound-related alterations in hematological parameters at any time point. The MRL of 0.1 mg/kg/day was calculated by dividing the male rat NOAEL of 9.6 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). The lack of quantitative information regarding incidences of non-neoplastic lesions precludes the use of BMD methodology for MRL derivation.

Dose and end point used for MRL derivation: 9.6 mg/kg/day; NOAEL for liver effects in rats.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

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

Was a conversion used from ppm in food or water to a mg/body weight dose? A conversion was done by the investigators.

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

Other additional studies or pertinent information which lend support to this MRL: The NOAEL and LOAEL for liver effects from Kociba et al. (1974) are supported by the results of Kano et al. (2009). In that study, groups of F344/DuCrj rats (50/sex/dose level) received 1,4-dioxane in the drinking water for 104 weeks. 1,4-Dioxane was administered at levels of 0, 200, 1,000, and 5,000 ppm for 2 years (0, 11, 55, and 274 mg/kg/day for males; 0, 18, 83, and 429 mg/kg/day for females). End points evaluated included clinical signs, food and water consumption, body and organ weights, and gross and microscopic examination of major organs and tissues. Terminal body weight was reduced 9% in high-dose males (274 mg/kg/day) and 20% in high-dose females (429 mg/kg/day). In males, relative liver weight was significantly increased at 55 mg/kg/day (14%) and 274 mg/kg/day (72%). A significant increased incidence of mixed cell foci was observed in the liver from male rats dosed with ≥55 mg 1,4-dioxane/kg/day. Increased incidence of acidophilic and mixed cell foci were reported in the liver from high-dose females (429 mg/kg/day). In addition, both high-dose male (274 mg/kg/day) and female (429 mg/kg/day) rats had significantly increased incidence of nuclear enlargement and squamous cell metaplasia of the respiratory epithelium; females dosed with ≥83 mg 1,4-dioxane/kg/day also showed significantly increased incidence of nuclear enlargement of the nasal olfactory epithelium.

The NCI (1978) bioassay in Osborne-Mendel rats used somewhat higher dose levels than Kociba et al. (1974) and Kano et al. (2009), but did not observe liver lesions in male rats dosed with 240 mg 1,4-dioxane/kg/day, a dose level that caused liver hyperplasia in male F344 rats dosed with 81 mg/kg/day or that caused hepatocyte degeneration in Sherman rats dosed with 94 mg/kg/day. Since the dosing method was the same in the three studies, the drinking water, the different results may reflect differences in strain sensitivity.

Agency Contact (Chemical Manager): Sharon Wilbur

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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

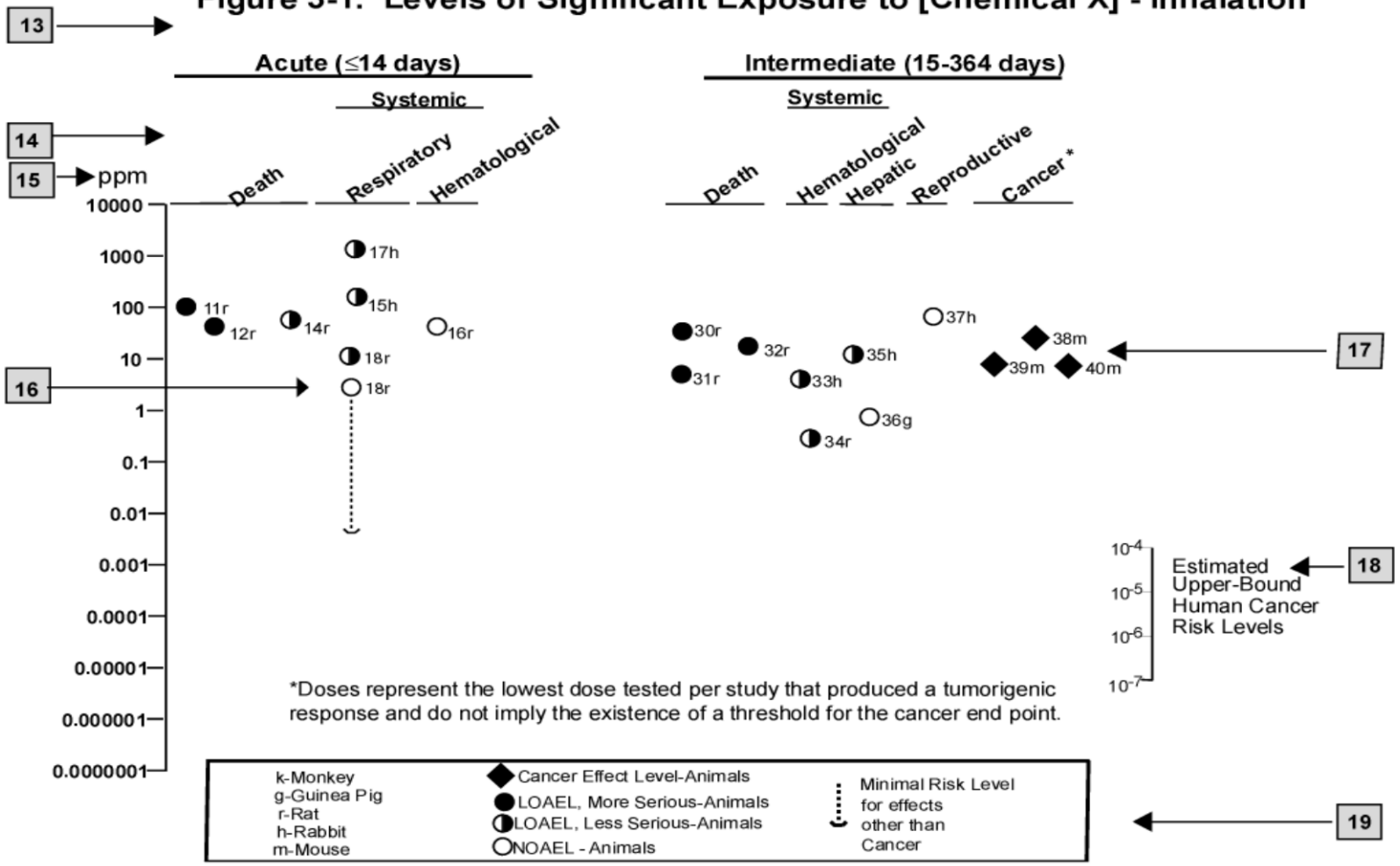
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	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



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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/IMCO	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. HEALTH ADVISORY

Health Advisory - An Overview for the Public

1,4-Dioxane

August 2007

Why is 1,4-dioxane currently a potential health concern?

Conflicting reports regarding 1,4-dioxane exposure from use of some bath and cosmetic products

Recent reports in the media about 1,4-dioxane contamination of children's bath products prompted ATSDR to reexamine its recommendations to families on reducing risks of exposure to 1,4-dioxane. **Note:** The acute effects described in this document are not likely to occur at concentrations of 1,4-dioxane that are normally found in the U.S. environment.

Why has the Agency for Toxic Substances and Disease Registry (ATSDR) provided this health advisory for 1,4-dioxane?

ATSDR provides trusted health information to the public

ATSDR's mission is to serve the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and disease related exposures to toxic substances.

What is 1,4-dioxane?

1,4-Dioxane is used in manufacturing and in household products

1,4-Dioxane (also called dioxane) is produced in large amounts (between 10 million and 18 million pounds in 1990) by three companies in the United States. Companies use dioxane:

- for a solvent for paper, cotton, and textile processing
- for chemical manufacturing, and
- in automotive coolant liquid.

APPENDIX D

How are people exposed to 1,4-dioxane?

Transmission through inhalation, ingestion, or skin contact

1,4-Dioxane enters the body when people breathe air or consume water or food contaminated with 1,4-dioxane. People can also be exposed following contact with cosmetics, shampoo, or bubble bath that contain certain ingredients in which 1,4-dioxane may be a contaminant. 1,4-Dioxane does not remain in the body because it breaks down into chemicals that are removed quickly.

Where is 1,4-dioxane found ?

Food	Traces of 1,4-dioxane can be ingested from: • some food supplements • food containing residues from packaging adhesives • food sprayed with pesticides containing 1,4-dioxane as a solvent or inert ingredient
Ground Water	A few communities' water supplies are contaminated with 1,4-dioxane. Information on the concentrations of 1,4-dioxane in groundwater, surface waters and drinking water are limited.
Household products	1,4-Dioxane may be present as a trace contaminant in household products such as: • shampoo • liquid dishwashing soap • baby lotion • hair lotions • bath foam • and other cosmetic products
Industrial solvents	1,4-Dioxane is primarily used as an industrial solvent in several manufacturing processes.
Spermicidal agents	1,4-Dioxane is found in some over-the-counter spermicidal sponges.

APPENDIX D

What are the health effects of 1,4-dioxane exposure?

Effects of 1,4-dioxane on human health and the environment depend on how much 1,4-dioxane is present and the length and frequency of exposures. **Note:** The acute effects described below are not likely to occur at concentrations of 1,4-dioxane that are normally found in the U.S. environment.

Short-term exposure to 1,4-dioxane

- Breathing: 1,4-Dioxane for short periods of time causes irritation of the eyes, nose and throat in humans. Exposure to large amounts of 1,4-dioxane can cause kidney and liver damage.
- Accidental worker exposure to large amounts of 1,4-dioxane has resulted in several deaths. Symptoms associated with these industrial deaths suggest 1,4-dioxane causes adverse nervous system effects.

Long-term exposure to 1,4-dioxane

- Animal studies: Laboratory studies show that repeated exposure to large amounts of 1,4-dioxane in drinking water, in air, or on the skin causes liver and kidney damage in animals Laboratory studies also show that oral exposure to 1,4-dioxane over a lifetime causes cancer in animals. Skin exposure of animals to 1,4-dioxane has shown that it can increase the cancer-causing properties of other chemicals.
- Human studies: There is little specific information regarding the non-cancer outcomes in workers following repeatedly breathing small amounts of 1,4-dioxane over long periods of time.
- Cancer classifications: (based on inadequate evidence in humans and sufficient evidence in animals):
    - Department of Health and Human Services (HHS) considers 1,4-dioxane as reasonably anticipated to be a human carcinogen.
    - Environmental Protection Agency (EPA) established that 1,4-dioxane is a probable human carcinogen.
    - International Agency for Research on Cancer (IARC) has determined that 1,4-dioxane is possibly carcinogenic to humans.

Reproductive health/infants and 1,4-dioxane

- Miscarriage and stillbirths: There are studies that show elevated rates of spontaneous abortion and stillbirths associated with occupational exposure to a combination of chemicals that included 1,4-dioxane, but the role of 1,4-dioxane, if any, is unknown.
- Breast milk transfer: A nursing mother exposed to a high amount of 1,4-dioxane might pass it to the infant through her breast milk. This concern is based on scientific models, not on actual data from the breast milk of women exposed to 1,4-dioxane.

Is there a medical test to show whether I've been exposed to 1,4-dioxane?

1,4-Dioxane and its breakdown products can be measured in your blood and urine

1,4-Dioxane and its breakdown products can be measured in your blood and urine, and positive results indicate you have been exposed to 1,4-dioxane. The tests are not routinely available at your doctor's office because they require special equipment, but the doctor can collect the samples and send them to a special laboratory. The tests need to be conducted within days after the exposure because 1,4-dioxane and its breakdown products leave the body fairly rapidly. These tests do not predict whether exposure to 1,4-dioxane will produce harmful health effects.

What levels of 1,4-dioxane are considered acceptable by regulatory agencies?

1,4-Dioxane levels in food set by the Food and Drug Administration (FDA)

- The National Academy of Sciences (NAS) specified a maximum limit of 10 ppm (parts per million) for 1,4-dioxane in the ingredient polysorbate, a food additive (NAS 2003).
- FDA also set a limit on 1,4-dioxane at 10 ppm in approving glycerides and polyglycerides in products such as dietary supplements. This regulation is located at 21 CFR 172.736. The FDA regulation for 1,4-dioxane as an indirect food additive is also 10 ppm and refers to its use as an adhesive component in packaging material.

1,4-Dioxane levels in cosmetics-voluntary cooperation

- FDA's regulatory legal authority over the cosmetics is different from other products regulated by the agency such as drugs, biologics, and medical devices. Consequently, FDA must rely, in part, on voluntary industry cooperation.
- Whereas the press has recently reported that FDA recommends 10 ppm for 1,4-dioxane in cosmetic products, the FDA does not have a recommendation for 1,4-dioxane in cosmetic products.

1,4-Dioxane levels in ground water

- The Environmental Protection Agency (EPA) recommends that the levels of 1,4-dioxane in drinking water that children drink for 1 day not exceed 4 milligrams per liter (mg/L) or 0.4 mg/L, if they drink water for 10 days. However, EPA has not established a federal drinking water standard (maximum contaminant level or MCL).

What do studies show about the levels of 1,4-dioxane in shampoos and bubble baths?

Note: Much of the information in this section is from: Black RE, Hurley FJ, Havery DC. 2001. Occurrence of 1,4-dioxane in cosmetic raw materials and finished cosmetic products. J AOAC Int 84(3):666-670.

1979: 1,4-Dioxane identified in raw materials used in the manufacture of cosmetic products

In 1979-1980, the FDA urged the cosmetic industry to monitor their raw materials for 1,4-dioxane.

1980s- Downward trend in levels of 1,4-dioxane.

The results of surveys suggested a downward trend in the levels of 1,4-dioxane in cosmetic finished products analyzed between 1981 and 1984. Changes in the manufacturing process may be responsible for the apparent trend. FDA surveys were then suspended in 1984 but were resumed in 1992.

1990s- Levels increase

Ninety-nine products were analyzed between 1992 and 1997. The products analyzed since 1994 focused on children's shampoos because the process used in their manufacturing was linked to 1,4-dioxane. The downward trend in the levels of 1,4-dioxane previously observed in products analyzed in the 1980s was no longer evident in the products analyzed in the 1990s. Of particular concern were levels of 1,4-dioxane observed in children's shampoos analyzed in 1994/95 manufactured by two companies. 1,4-Dioxane was frequently present at levels in excess of 85 ppm.

Can high levels of 1-4-dioxane be avoided in cosmetics, bath products and shampoos?

High levels can be avoided

The low levels of 1,4-dioxane observed in some raw materials and finished products demonstrate that with current technology, excessive levels of 1,4-dioxane are avoidable. Continued periodic monitoring of cosmetic ingredients and cosmetic finished products for the presence of 1,4-dioxane is necessary.

What can I do to ensure that my family is not exposed to 1,4-dioxane?

Check ingredients listed on product packaging

Given the expanding range of consumer products that may contain 1,4-dioxane as a contaminant, families should exercise caution in selecting products that do not clearly specify the ingredients that contain 1,4-dioxane.

The ingredients that may be listed on cosmetics, detergents, and shampoos include:

- polyethylene glycol (PEG),
- polyethylene,
- polyoxyethylene,
- or oxynol-

These ingredients are most likely to contain 1,4-dioxane.

Where can I find more information regarding 1,4-dioxane?

Document	Source
ATSDR ToxFAQs	http://www.atsdr.cdc.gov/toxfaqs/TF.asp?id=954&tid=199
EPA dioxane fact sheets	http://www.epa.gov/opptintr/chemfact/dioxa-sd.txt http://www.epa.gov/chemfact/dioxa-fs.pdf
FDA: Cosmetics	Cosmetic Handbook. 1992. U.S. Food and Drug Administration. Center for Food Safety and Applied Nutrition. FDA/IAS Booklet: 1992.
FDA: Food Additives	FDA's website at http://www.fda.gov/Food/FoodIngredientsPackaging/ucm115333.htm.
National Industrial Chemicals Notification and Assessments System	http://www.nicnas.gov.au/publications/car/pec/pec7/pec7_full_report_pdf.pdf This is a full public report on 1,4-dioxane from the National Industrial Chemicals Notification and Assessments Scheme.

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APPENDIX E. INDEX