APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences (proposed), 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 Human Health Sciences (proposed), 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: Tris(2-chloroethyl) phosphate (TCEP)
CAS Numbers: 115-96-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 23
Species: Rat

Minimal Risk Level: 0.6 [X] mg/kg/day [ ] ppm

Reference: NTP. 1991a. NTP toxicology and carcinogenesis studies of tris(2-chloroethyl) phosphate (CAS No. 115-96-8) in F344/N rats and B6C3F$_1$ mice (gavage studies). Program NT. TR 391. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr391.pdf. May 6, 2009.

Experimental design: Groups of Fischer-344 rats (10/sex/dose) were administered 0, 22, 44, 88, 175, or 350 mg TCEP by gavage in corn oil 5 days/week for 16 weeks (females) or 18 weeks (males). End points examined included clinical signs, body weight, serum cholinesterase activity, organ weight, gross necropsy, and histopathology of tissues and organs (control and highest dose group). The brain and kidneys of mid-dose (88 mg/kg/day) females were also examined microscopically.

Effect noted in study and corresponding doses: Two females in each the 175 and 350 mg/kg/day groups died on week 4 due to overdosing that week; others in these groups showed ataxia, convulsions, excessive salivation, and gasping. Females receiving 175 and 350 mg/kg/day experienced occasional periods of hyperactivity after dosing. High-dose females showed periodic convulsions during week 12. At termination, serum cholinesterase was reduced by 25 and 41% in females treated with 175 and 350 mg/kg/day, respectively; serum cholinesterase activity in males was comparable among groups. Final absolute and relative (to body weight or brain weight) weight of the liver and kidney of treated males and females were increased relative to controls (>10% at 175 mg/kg/day). At termination, serum cholinesterase was reduced by 25 and 41% in females treated with 175 and 350 mg/kg/day, respectively; cholinesterase in males was comparable among groups. There were no gross lesions due to treatment. However, necrosis of neurons of the hippocampus was seen in 10/10 females and in 2/10 males treated with 350 mg/kg/day, and in 8/10 females treated with 175 mg/kg/day. The affected neurons were mainly in the dorsomedial portion of the pyramidal row of the hippocampus. The more severe lesions showed mineral deposits in the affected areas. High-dose females also showed neuronal necrosis in the thalamus. The dose of 88 mg TCEP/kg/day is a NOAEL for brain lesions in female rats.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 85.07 mg/kg/day for brain lesions in female rats.

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

Uncertainty Factors used in MRL derivation:

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

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

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? Yes, the test chemical was administered 5 days/week; therefore, the $BMDL_{10}$ of 85.07 mg/kg/day was adjusted for continuous exposure by multiplying by 5 and dividing by 7 yielding a duration-adjusted $BMDL_{10}$ of 60.76 mg/kg/day.

Other additional studies or pertinent information that lend support to this MRL: Only three studies were available for review. NTP (1991a) also conducted studies in $B6C3F_1$ mice and reported that no brain lesions were observed in mice treated with up to 700 mg TCEP/kg/day for 16 weeks. Similar doses were tested in CD-1 mice in a reproductive study that used a continuous breeding protocol, and no brain lesions were reported in that study (NTP 1991b). In the reproductive study, the lowest dose tested, 175 mg TCEP/kg/day, caused a significant reduction in the number of live F_2 male pups per litter. In a 90-day study in male and female Sprague-Dawley rats administered up to 586 mg TCEP/kg/day via the diet, no brain lesions were reported (Anonymous 1977). However, it is unclear in the report available whether the brain was examined microscopically. No adverse effects were reported in that study, including hematology and clinical chemistry parameters, and histopathology of organs and tissues.

Modeling of the changes in absolute kidney weight in female rats proved unsuccessful as an adequate fit could not be obtained with any model. However, if the changes in absolute kidney weight in female rats in the NTP (1991a) study had been used as basis for MRL derivation using a NOAEL/LOAEL approach, the NOAEL would have been 88 mg TCEP/kg/day (<10% increase in kidney weight). The next highest dose, 175 mg/kg/day induced a 16% increase in absolute kidney weight. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the duration-adjusted NOAEL of 62.86 mg/kg/day (88 mg/kg/day x 5/7) would have resulted in an MRL of 0.6 mg/kg/day for TCEP, which supports the MRL derived using the BMD approach using the data set for brain lesions.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

APPENDIX A

BENCHMARK MODELING OF BRAIN LESIONS IN FEMALE RATS

Incidence data for brain lesions in female rats exposed to TCEP (NTP 1991a) were analyzed using the BMD approach for MRL derivation (Table A-1). Models in the EPA BMDS (version 2.1) were fit to the brain lesions data to determine a potential point 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 dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body weight, in the absence of a clear criteria as to what level of change in body/organ weight or body weight gain should be considered adverse, the BMR is defined as a change in weight or weight gain equal to 1 SD from the control mean (EPA 2000).

Table A-1. Incidence of Hippocampal Necrosis in Female Rats Exposed to TCEP for 16 Weeks

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	10	0
22	10	0
44	10	0
88	10	0
175	10	8
350	10	10

Source: NTP 1991a

Table A-2. Model Predictions for Necrosis of Hippocampal Neurons in Female Rats Exposed to TCEP for 16 Weeks

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	5	0.28	1.00	-0.49	0.20	-0.49	12.52	106.78	80.41
Logistic	4	0.00	1.00	0.00	0.00	0.00	14.01	160.02	88.23
LogLogistic[d,e]	**5**	**0.00**	**1.00**	**-0.013**	**0.00**	**-0.013**	**12.01**	**143.41**	**85.07**
LogProbit[d]	4	0.00	1.00	0.00	0.00	0.00	14.01	140.11	84.26
Multistage (1-degree)[f]	5	13.21	0.02	-1.1	-1.52	-2.3	33.31	ND(LS)	ND(LS)
Multistage (2-degree)[f]	5	5.08	0.41	-0.81	-1.70	-1.70	20.35	56.58	41.38
Multistage (3-degree)[f]	5	2.35	0.80	-0.42	-1.28	-1.28	16.02	77.77	59.06
Multistage (4-degree)[f]	5	1.12	0.95	-0.96	0.37	0.96	14.04	91.96	69.76
Multistage (5-degree)[f]	5	0.54	0.99	-0.70	0.19	0.19	13.04	103.04	76.30
Probit	4	0.00	1.00	0.00	0.00	0.00	14.01	147.06	85.11
Weibull[c]	4	0.00	1.00	-0.01	0.00	-0.01	14.01	149.30	84.03

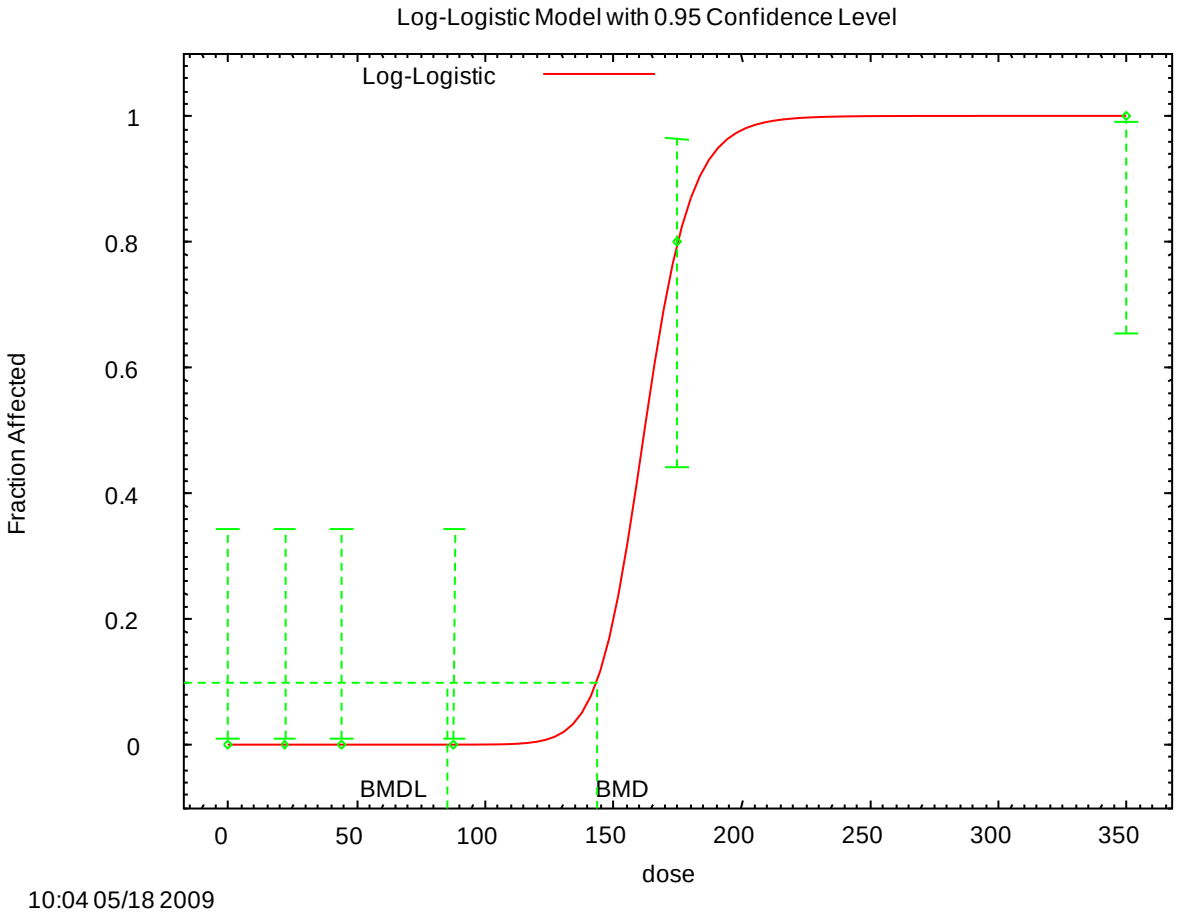
[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models (except for the Multistage 1-degree) provided adequate fit to the data. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.
[f]Betas restricted to ≥0.

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

Source: NTP 1991a

Based on these criteria, a Log-logistic model provided the best fit to the data (Table A-2). From this model, the predicted doses associated with a 10% extra risk (BMD_{10}) for brain lesions in female rats was 143.41 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 85.07 mg/kg/day (Figure A-1). Modeling the decrease in the number of live F_2 male pups per litter reported in the NTP (1991b) study resulted in the Linear (constant variance) model providing the best fit with a BMD_{10} and $BMDL_{10}$ of 242.19 and 167.83 mg/kg/day, respectively, considerably higher than the values obtained in the analysis of the brain lesions in female rats.

Figure A-1. Predicted and Observed Incidence of Brain Lesions in Female Rats Exposed to TCEP for 16 Weeks



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(2-chloroethyl) phosphate (TCEP)
CAS Numbers: 115-96-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 34
Species: Rat

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

Reference: NTP. 1991a. NTP toxicology and carcinogenesis studies of tris(2-chloroethyl) phosphate (CAS No. 115-96-8) in F344/N rats and B6C3F_1 mice (gavage studies). Program NT. TR 391. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr391.pdf. May 6, 2009.

Experimental design: Groups of Fischer-344 rats (60 rats/sex/dose) were administered 0, 44, or 88 mg TCEP/kg/day by gavage in corn oil 5 days/week for 104 weeks. End points examined included clinical signs, body weight, organ weight, gross necropsy, and histopathology of all major tissues and organs at interim kill (week 66, 10 rats/sex/group) and at termination. Hematology and clinical chemistry tests were conducted at interim kill.

Effect noted in study and corresponding doses: There were no clinical signs attributable to administration of TCEP or effects on body weight. Survival was reduced in high-dose males and females. Females that died early frequently had brain lesions, males did not. There were no chemical-related alterations in clinical chemistry and hematology parameters at week 66. Interim necropsy revealed a significant increase in absolute and relative liver and kidney weights in high-dose males. At termination, one of the principal nonneoplastic alterations attributed to administration of TCEP was a significant increase in renal tubule epithelial hyperplasia in the convoluted tubules of the cortex in high-dose males and females. The lesions were focal or multifocal and were characterized by stratification of the epithelial cells with partial to complete obliteration of the tubule lumens. In addition to the kidneys lesions, high-dose female rats showed degenerative lesions in the brain. The degenerative lesions were located in the cerebral cortex and brain stem, involved both the gray and white matter, and were focally distributed. Specifically, the lesions were in the thalamus, hypothalamus, basal ganglia, and frontal and parietal cortex. Other affected structures included the cingulate cortex, olfactory cortex, superior colliculus, hippocampus, geniculate body, globus pallidus, ventral pallidum, and amygdaloid nuclear region. The lesions varied in severity from minimal to marked, and often involved extensive areas. Active lesions were characterized by degeneration and necrosis with hemorrhage, while resolving lesions exhibited loss of neurons and neuropil, proliferation of glial cells, capillary hyperplasia, hypertrophy of the tunica media of small vessels, and hemosiderin-laden macrophages. Brain lesions were already observed at the 66-month interim kill. Incidences of lesions in specific areas ranged from 24 to 38%. The lesion with the highest incidence was cerebrum gliosis with an incidence of 19/50 (38%); the incidences in the control and low-dose groups were 0/50 and 0/49, respectively. A NOAEL of 44 mg/kg/day was defined for renal tubule epithelial hyperplasia in male and female rats and for cerebrum gliosis in female rats.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 32.82 mg/kg/day for renal tubule epithelial hyperplasia in female rats.

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

Uncertainty Factors used in MRL derivation:

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

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

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? Yes, the test chemical was administered 5 days/week; therefore, the $BMDL_{10}$ of 32.82 mg/kg/day was adjusted for continuous exposure by multiplying by 5 and dividing by 7 yielding a duration-adjusted $BMDL_{10}$ of 23.44 mg/kg/day.

Other additional studies or pertinent information that lend support to this MRL: The NTP (1991a) study was the only chronic-duration oral study available for TCEP. The $BMDL_{10}$ for cerebrum gliosis in female rats was somewhat higher (59.86 mg/kg/day) than that obtained for the renal tubular hyperplasia in both male and female rats; therefore, the MRL derived based on renal lesion is protective of brain lesions.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF RENAL TUBULE HYPERPLASIA IN FEMALE RATS

Incidence data for renal tubule epithelial hyperplasia in female rats exposed to TCEP (NTP 1991a) were analyzed using the BMD approach for MRL derivation (Table A-3). Models in the EPA BMDS (version 2.1) were fit to the brain lesions data to determine a potential point 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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body/organ weight or weight gain, in the absence of a clear criteria as to what level of change should be considered adverse, the BMR is defined as a change equal to 1 SD from the control mean (EPA 2000).

Table A-3. Incidence of Renal Tubule Epithelial Hyperplasia in Rats Exposed to TCEP for 2 Years

Dose (mg/kg/day)	Total number of rats	Males with lesions	Females with lesions
0	50	0	0
44	50	2	3
88	50	24	16

Source: NTP 1991a

Based on the criteria mentioned above, the Multistage (2-degree) model best fit the data. From this model, the predicted doses associated with a 10% extra risk (BMD_{10}) for renal tubule hyperplasia in female rats was 48.00 mg/kg/day; the lower 95% confidence limit on this dose ($BMDL_{10}$) was 32.82 mg/kg/day (Figure A-2). Modeling the data set for renal tubule hyperplasia in male rats resulted in the Log logistic model providing the best fit with a BMD_{10} and $BMDL_{10}$ of 54.80 and 43.58 mg/kg/day, respectively, only slightly higher than the values obtained in the analysis of the lesions in female rats. Modeling the data set for cerebrum gliosis in female rats resulted in the Log logistic model providing the best fit with a BMD_{10} and $BMDL_{10}$ of 80.04 and 59.86 mg/kg/day, respectively. Therefore, the MRL based on renal lesions is protective of brain lesions.

Table A-4. Model Predictions for Incidence of Renal Tubule Epithelial Hyperplasia in Female Rats Exposed to TCEP for 2 Years

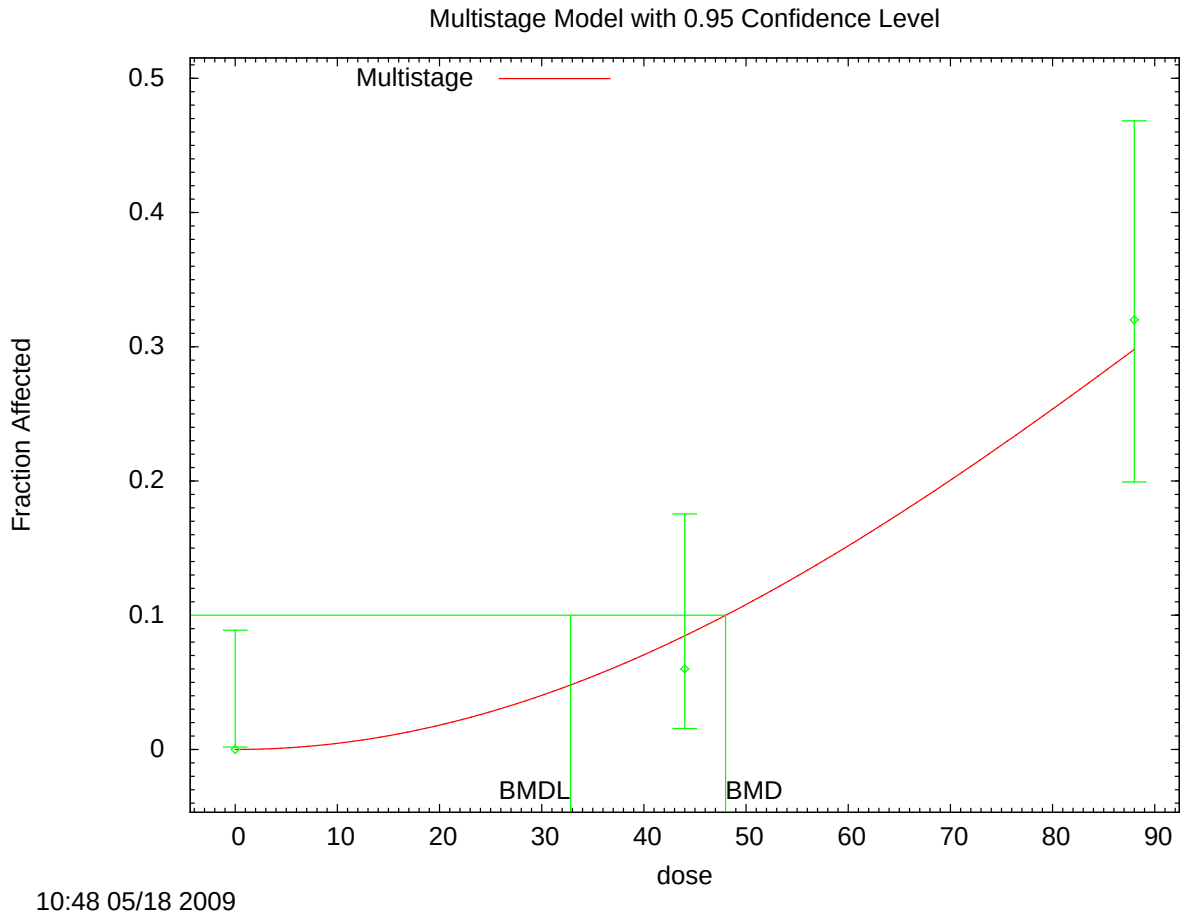
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]: Dose below BMD	Scaled residuals[b]: Dose above BMD	Scaled residuals[b]: Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	1	0.00	1.00	0.00	0.00	0.00	89.38	53.09	36.09
Logistic	1	0.41	0.52	0.36	-0.08	-0.53	90.06	60.16	49.51
LogLogistic[d]	1	0.00	1.00	0.00	0.00	0.00	89.38	53.33	36.29
LogProbit[d]	1	0.00	1.00	0.00	0.00	0.00	89.38	52.37	37.59
Multistage (1-degree)[e]	2	3.66	0.16	0.00	-1.54	-1.54	91.51	32.13	22.50
Multistage (2-degree)[e,f]	**2**	**0.51**	**0.78**	**-0.63**	**0.34**	**-0.63**	**87.93**	**48.00**	**32.82**
Probit	1	0.20	0.66	0.24	-0.08	-0.36	89.71	57.32	46.59
Weibull[c]	1	0.00	1.00	0.00	0.00	0.00	89.38	53.83	35.90

[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. All models provided adequate fit to the data. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

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

Source: NTP 1991a

Figure A-2. Predicted and Observed Incidence of Renal Tubule Hyperplasia in Female Rats Exposed to TCEP for 2 Years



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tributyl phosphate (TnBP)
CAS Numbers: 126-76-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 13
Species: Rat

Minimal Risk Level: 1.1 [X] mg/kg/day [ ] ppm

Reference: Noda T, Yamano T, Shimizu M, et al. 1994. Effects of tri-n-butyl phosphate on pregnancy in rats. Food Chem Toxicol 32(11):1031-1036.

Experimental design: Groups of Wistar rats (20 rats/sex/dose level) were administered 0, 62.5, 125, 250, or 500 mg TnBP/kg/day by gavage in corn oil on Gd 7–17. Clinical signs, body weight, and food consumption were monitored. The rats were euthanized on Gd 20. The gravid uterus, the position and number of living and dead fetuses in the uterus, including resorbed fetuses in the uterus, the number of corpora lutea, and maternal liver, kidneys, and spleen weights were recorded. The living fetuses were examined for their sex and external malformation, and then weighed. Skeletal abnormalities were evaluated in half of the fetuses, whereas the other half was evaluated for visceral abnormalities.

Effect noted in study and corresponding doses: Rats exposed to 500 mg TnBP/kg/day showed piloerection, wetting of abdominal hair with urine, and salivation during treatment, but these signs disappeared after the last treatment. Final maternal weight was reduced 6–9% in the two highest dose groups. Adjusted body weight gain (weight gain from Gd 0 to 20 minus gravid uterus weight) was reduced 13% at 125 mg/kg/day, 39% at 250 mg/kg/day, and 63% at 500 mg/kg/day. Absolute liver and kidney weight in treated rats was not affected (<10% change relative to controls). Spleen weight was reduced 11% at 500 mg/kg/day. Gravid uterus weight was not affected by treatment. All pregnant rats had fetuses on Gd 20. There were no significant differences between the groups in any of the developmental parameters evaluated. There was only one malformation occurring in the 125 mg/kg/day dose group and consisted of conjoined twins. No visceral anomalies were reported. Based on a significant reduction in maternal body weight gain at ≥125 mg/kg/day, a maternal NOAEL and LOAEL of 62.5 and 125 mg/kg/day, respectively, were defined in this study; the highest dose tested, 500 mg/kg/day was a developmental NOAEL.

Dose and end point used for MRL derivation: $BMDL_{1SD}$ of 111.47 mg/kg/day for decrease weight gain in pregnant rats on Gd 0–20.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty Factors used in MRL derivation:

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

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

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.

Other additional studies or pertinent information that lend support to this MRL: Only one additional study was a potential source of data for MRL derivation. In that study, groups of Sprague-Dawley rats (10/sex/group) were administered 0, 137, or 411 mg TnBP/kg/day by gavage on 14 consecutive days (Laham et al. 1984b). End points examined included clinical signs, body weight, hematological and clinical chemistry tests, and histological examinations of the brain, heart, kidneys, liver, lungs, spleen, ovaries, and testes. Significant findings in high-dose rats included decreased hemoglobin in females, increased absolute and relative liver weight in males and females, increased serum potassium in females, decreased absolute and relative spleen weight, and degenerative changes in the testes. A study of limited scope reported decreased nerve conduction velocity accompanied by morphological alterations in the sciatic nerve of rats dosed with 411 mg TnBP/kg/day for 14 days; the NOAEL was 274 mg TnBP/kg/day (Laham et al. 1983).

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APPENDIX A

BENCHMARK MODELING OF REDUCED WEIGHT GAIN IN PREGNANT RATS

Data from Noda et al. (1994) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) to determine potential points of departure for the MRL (Table A-5).

Table A-5. Data for the Change in Adjusted Body Weight Gain on Gestation Days 0–20 Exposed to TnBP on Gestation Days 7–17

Dose (mg/kg/day)	Number of animals tested	Body weight gain (g)	SD
0	20	38.0	7.46
62.5	20	37.2	8.27
125	20	33.2	8.98
250	20	23.0	6.51
500	20	9.4	8.56

Source: Noda et al. 1994

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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body/organ weight or weight gain, in the absence of a clear criteria as to what level of change should be considered adverse, the BMR is defined as a change equal to 1 SD from the control mean (EPA 2000). Based on the criteria for model selection, the Linear model provided the best fit (Table A-6 and Figure A-3).

Table A-6. Model Predictions for TnBP, Change in Body Weight Gain on Gestation Days 0–20

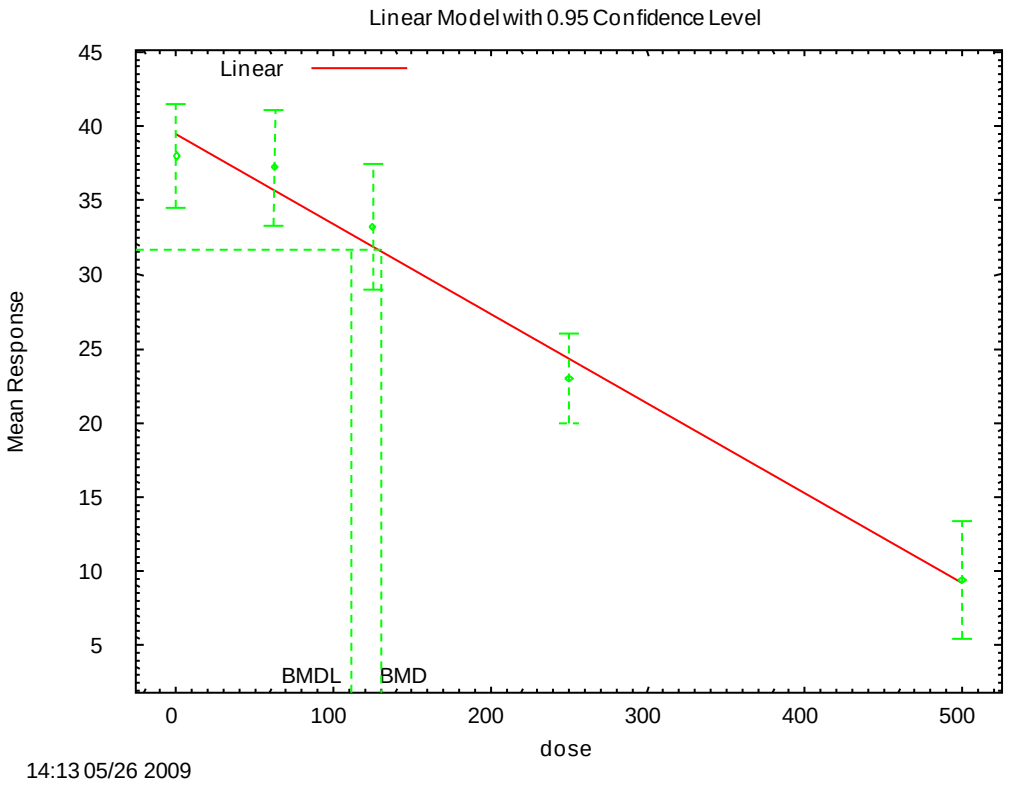
Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Constant variance									
Hill[d]	<0.0001	0.65	0.86	-0.08	0.02	0.13	520.89	162.91	113.67
Linear[e,f]	**<0.0001**	**0.65**	**0.46**	**0.71**	**-0.78**	**-0.87**	**519.44**	**130.32**	**111.47**
Polynomial (2-degree)[e]	<0.0001	0.65	0.28	0.66	-0.86	-0.86	521.43	133.85	111.53
Power[d]	<0.0001	0.65	0.31	0.52	-1.01	-1.01	521.19	145.15	112.27

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model provided adequate fit to variance data. With constant variance model applied, all models (except for the Hill) provided adequate fit to means. Since the range of BMDLs was <3-fold, the model with lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1 SD = change is 1 standard deviation from the control mean); BMR = benchmark response; DF = degrees of freedom

Source: Noda et al. 1994

Figure A-3. Fit of Linear Model (Constant Variance) to Data on Body Weight Gain on Gestation Days 0–20 in Rats Exposed to TnBP on Gestation Days 7–17



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tributyl phosphate (TnBP)
CAS Numbers: 126-76-8
Date: April 2012
Profile Status: Draft 2, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 22
Species: Rat

Minimal Risk Level: 0.08 [X] mg/kg/day [ ] ppm

Reference: Arnold LL, Christenson WR, Cano M, et al. 1997. Tributyl phosphate effects on urine and bladder epithelium in male Sprague-Dawley rats. Fundam Appl Toxicol 40(2):247-255.

Experimental design: Groups of male Sprague-Dawley rats (20 in the control and high-dose group, 10 in the low- and mid-dose groups) were fed a diet containing 0, 200, 700, or 3,000 ppm TnBP for 10 weeks. This corresponds to doses of approximately 0, 9, 33, or 143 mg TnBP/kg/day based on a similar study in male Sprague-Dawley rats exposed to the same dietary concentrations of TnBP (Auletta et al. 1998a). End points examined included clinical signs, body weight, food consumption, urinalysis, and histological examination (10 rats per group at termination) of the stomach, kidneys, and urinary bladder. To evaluate the effect of urine acidification, an additional group of rats received 3,000 ppm TnBP plus 12,300 ppm ammonium chloride. Yet another group received ammonium chloride alone. Reversibility of the effects of TnBP was examined in a group of 10 rats kept on a control diet for 10 weeks after the 10-week treatment period.

Effect noted in study and corresponding doses: There were no clinical signs attributable to TnBP. Mean final weight of the high-dose group was reduced >10% relative to controls; food consumption was not significantly affected. During the recovery period, body weight of the high-dose recovered to control levels. Urinary parameters on week 11 among treated groups were comparable to controls except for osmolality and creatinine, which were significantly lower in the high-dose group than in controls, indicating a dilutional effect. Urinary pH in the groups receiving ammonium chloride was 6.0 compared to $\geq$ 7.5 in the other groups. There was no evidence of an amorphous precipitate, abnormal microcrystals, or calculi in the urine from individual rats. Crystals were present in the control and TnBP-treated rats. Treatment with TnBP caused urinary bladder hyperplasia in mid-and high-dose rats, with severity that was dose-related, reversible, and less severe in the rats dosed also with ammonium chloride. Incidences were 0/10, 0/10, 8/10, and 10/10 with increasing doses (see also Table A-7 below). There were no histological alterations in the stomach or kidneys. A NOAEL of 9 mg TnBP/kg/day for urothelial hyperplasia was defined in this study; the LOAEL was 33 mg/kg/day.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 8.03 mg/kg/day for urinary bladder hyperplasia in male rats dosed in the diet for 10 weeks.

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

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes, doses were estimated based on a similar study in male Sprague-Dawley rats exposed to the same dietary concentrations of TnBP (Auletta et al. 1998a).

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.

Other additional studies or pertinent information that lend support to this MRL: The urinary bladder was also the most sensitive tissue in two additional intermediate-duration studies. Increased incidence of urinary bladder hyperplasia was reported in male and female rats in a 3-month dietary study (FMC 1985a); the NOAEL was 13.8 mg TnBP/kg/day and the LOAEL was 68.1 mg TnBP/kg/day. Tyl et al. (1997) reported similar results in F_0 and F_1 male and female rats dosed with approximately 51 mg TnBP/kg/day in a 2-generation reproductive study; the NOAEL was 15 mg TnBP/kg/day (see Table A-7).

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF URINARY BLADDER HYPERPLASIA IN RATS

Incidence data for urothelial hyperplasia in male rats from the Arnold et al. (1997) study, for urothelial hyperplasia in F_0 males and females from the Tyl et al. (1997) study, and for urothelial hyperplasia in males from the FMC 1985a) study were analyzed using the BMD approach for MRL derivation. Incidences are shown in Table A-7. The results form the Arnold et al. (1997) model fit are shown in Table A-8; the FMC (1985a) and Tyl et al. (1997) model fit results are not shown. The data set from Tyl et al. (1997) corresponds to incidences in the parental generation (F_0). Incidences in F_1 females were virtually the same as in F_0 females, whereas incidences in mid-dose F_1 males were slightly lower than in F_0 males. Also included in Table A-7 is the data set from the 2-year study of Auletta et al. (1998a). The results from fitting the Auletta (1998a) data to various BMDL models are shown in Table A-9 (male rats) and Table A-10 (female rats) on pages A-24 and A-25, respectively, with the chronic MRL worksheet. Only the best fit $BDML_{10}$ value from each of the various studies is included in the summary Table A-7.

Table A-7. Incidence of Urinary Bladder Hyperplasia Induced by TnBP in Four Studies in Rats

				NOAEL	LOAEL		$BMDL_{10}$
Arnold et al. (1997)–10 weeks							
Dose (mg/kg/day)	0			9	33	143	
Males	0/10			0/10	8/10	10/10	**8.03**
FMC (1985a)–13 weeks							
Dose (mg/kg/day)	0.12	0.6	2.8	13.8	68.1	360	
Males	0/10	0/10	0/10	0/10	10/10	10/10	12.61
Tyl et al. (1997)–10 weeks							
Dose (mg/kg/day)	0			15	51	217	
Males	0/30			1/29	22/29	30/30	13.03
Females	0/30			2/29	21/30	30/30	9.12
Auletta et al. (1998a)–2 years							
Dose (mg/kg/day)	0			9	33	143	
Males	3/50			3/50	12/49	17/49	23.51
Females	1/50			1/50	5/49	29/49	53.59

$BMDL_{10}$ = The 95% lower confidence limit on the dose associated with a 10% extra risk; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Table A-8. Model Predictions for Incidence of Urinary Bladder Hyperplasia in Male Rats Exposed to TnBP for 10 weeks

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day
Gamma[c,d]	**3**	**0.00**	**1.00**	**-0.02**	**0.001**	**-0.02**	**12.01**	**19.74**	**8.03**
Logistic	2	0.00	1.00	0.00	0.00	0.00	14.01	28.80	10.49
LogLogistic[e]	2	0.00	1.00	0.00	0.00	0.00	14.01	26.21	8.27
LogProbit[e]	2	0.00	1.00	0.00	0.00	0.00	14.01	21.67	8.24
Multistage (1-degree)[f]	3	4.41	0.22	0.00	-1.83	-1.83	19.03	3.30	1.96
Multistage (2-degree)[f]	3	1.23	0.75	-1.03	0.40	-1.03	14.21	9.17	4.46
Multistage (3-degree)[f]	3	0.33	0.95	-0.56	0.12	-0.56	12.65	13.52	6.10
Probit	2	0.00	1.00	0.00	0.00	0.00	14.01	25.25	9.61
Weibull[c]	2	0.00	1.00	-0.013	0.00	-0.013	14.01	23.96	7.89

[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]Selected model. All models provided adequate fit to the data. The range of $BMDL_{10}$ values was >3-fold across all models, but much of this variation was due to the poorest fitting model, the 1-degree multistage. Ignoring the $BMDL_{10}$ from the 1-degree multistage model, the range of $BMDL_{10}$ values was <3-fold; thus, the model with the lowest AIC was selected (Gamma).
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

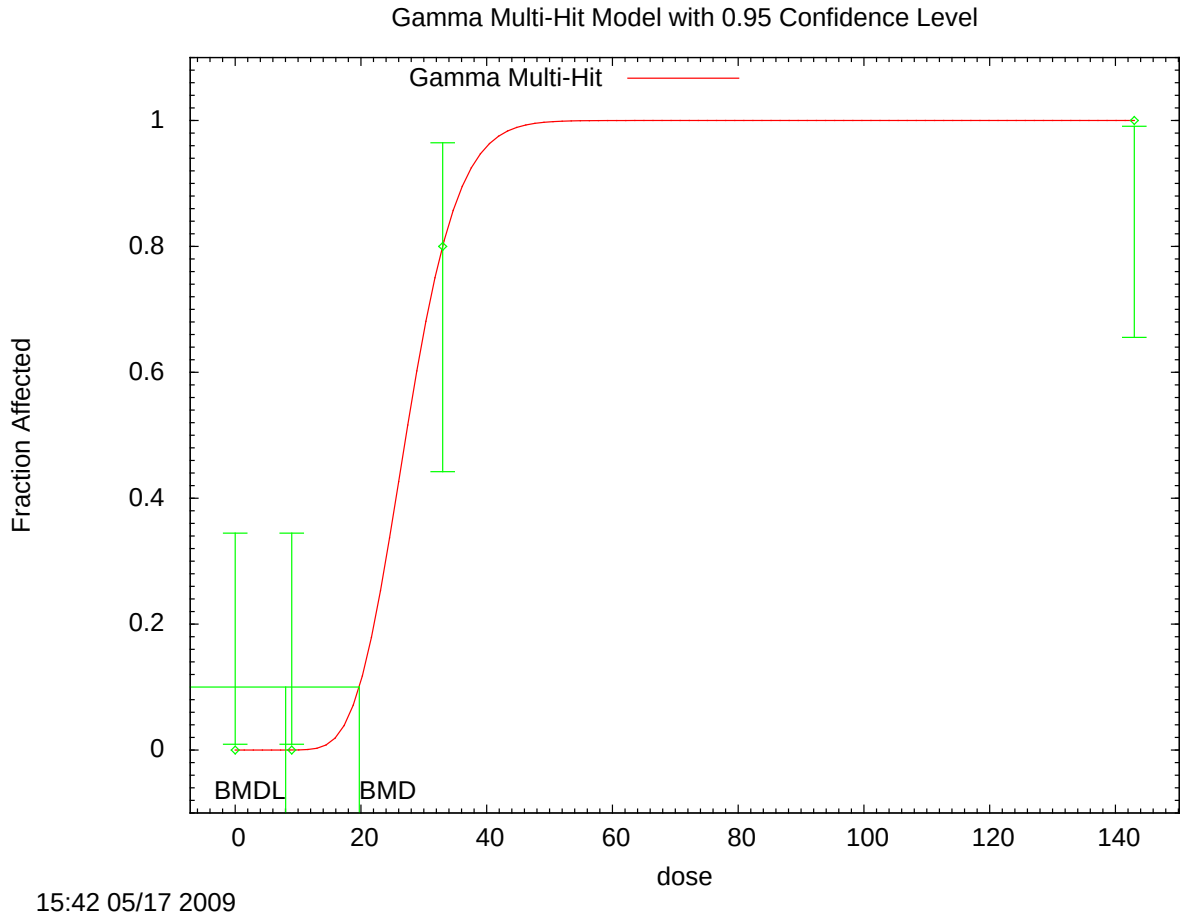
AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); BMR = benchmark response;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

Source: Arnold et al. 1997

Incidence data for urothelial hyperplasia in male rats from the Arnold et al. (1997) study, urothelial hyperplasia in F_0 males and females from the Tyl et al. (1997) study, and urothelial hyperplasia in male rats from the FMC (1985a) study were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to urothelial hyperplasia data to determine potential points of departure for the MRL. For the Arnold et al. (1997) data set, the range of $BMDL_{10}$ values for adequately fitting models (by the chi-square goodness of fit measure) varied by > 3-fold, but much of this variation was due to the relatively poor fit of the 1- and 2-degree multistage models. The range of $BMDL_{10}$ values from the remaining models was <2-fold and the model with the lowest AIC (Gamma) was selected as the best fitting model, predicting BMD_{10} and $BMDL_{10}$ values of 19.74 and 8.03 mg/kg/day. For the urinary hyperplasia data in F_0 males in the Tyl et al. (1997) study, the best fitting model predicted BMD_{10} and $BMDL_{10}$ values of 21.43 and 13.03 mg TnBP/kg/day, respectively; the predicted values for F_0 female rats were 15.42 and 9.12 mg TnBP/kg/day, respectively. For the FMC (1985a) data set, the range of $BMDL_{10}$ values for adequately fitting models (by the chi-square goodness of fit measure) varied by >3-fold, but much of this variation was due to the relatively poor fit of the 1-degree multistage model. The range of $BMDL_{10}$ values from the remaining models was <3-fold and the model with the lowest AIC (Weibull) was selected as the best fitting model, predicting BMD_{10} and $BMDL_{10}$ values of 49.87 and 12.61 mg/kg/day, respectively. Comparing across the four intermediate-duration data sets, the lowest $BMDL_{10}$ of 8.03 mg/kg/day for urinary bladder hyperplasia (Arnold et al. 1997) is selected as the point of departure for the MRL (Table A-8). Applying an uncertainty factor of 100 (10 for animal to human

extrapolation and 10 for human variability) to the $BMDL_{10}$ yields an intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP. The model fit is shown in Figure A-4.

Figure A-4. Fit of Gamma Model to Data on Incidence of Urinary Bladder Hyperplasia in Male Sprague-Dawley Rats Exposed to TNBP for 10 Weeks



Source: Arnold et al. 1997

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tributyl phosphate (TnBP)
CAS Numbers: 126-76-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Species: Rat

Minimal Risk Level: 0.08 [X] mg/kg/day [ ] ppm

Reference: Arnold LL, Christenson WR, Cano M, et al. 1997. Tributyl phosphate effects on urine and bladder epithelium in male Sprague-Dawley rats. Fundam Appl Toxicol 40(2):247-255.

It is recommended that the intermediate-duration oral MRL of 0.08 mg/kg/day for TnBP also be adopted as chronic-duration oral MRL, as explained below.

Only two chronic-duration oral studies were located for TnBP, one in rats (Auletta et al. 1998a) and one in mice (Auletta et al. 1998b). As in the intermediate-duration studies, the urinary bladder from rats was the most sensitive target for TnBP toxicity. Rats were dosed via the diet for 2 years, whereas mice were treated for 18 months. Male rats received doses of 0, 9, 33, or 143 mg TnBP/kg/day, whereas females received doses of 0, 12, 42, or 182 mg TnBP/kg/day. The doses for male and female mice were 0, 28.9, 169, or 585 mg/kg/day and 0, 24.1, 206, or 711 mg/kg/day, respectively. At termination, the incidences of trace to severe urinary bladder hyperplasia in male rats were 3/50, 3/50, 12/49, and 17/49 with increasing doses (see Table A-7 in the derivation of the intermediate-duration oral MRL). The corresponding incidences in female rats were 1/50, 1/50, 5/49, and 29/49. Urinary bladder hyperplasia was not observed in mice. Based on these findings, the increased incidence of urothelial hyperplasia in rats was used to determine a point of departure for derivation of a chronic-duration oral MRL for TnBP.

Incidence data for urinary bladder hyperplasia in male and female rats exposed to TnBP (Auletta et al. 1998a) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to the urinary bladder lesion 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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >2–3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Comparing across models using these criteria showed that the Multistage 1-degree model was the only model with an adequate fit for the incidence data in male rats, whereas the Probit model provided the best fit for the incidence data in female rats. This analysis yielded respective $BMDL_{10}$ values of 23.51 and 53.59 mg TnBP/kg/day (Tables A-9 and A-10).

Table A-9. Model Predictions for Incidence of Urinary Bladder Hyperplasia in Male Rats Exposed to TnBP for 2 Years

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]: Dose below BMD	Scaled residuals[b]: Dose above BMD	Scaled residuals[b]: Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Logistic	2	6.84	0.03	2.19	-0.32	2.19	173.60	ND(LS)	NS(LS)
LogLogistic[d,e]	1	20.68	0.00	-2.16	-2.16	-2.16	190.72	ND(LS)	NS(LS)
LogProbit[d]	2	20.68	0.00	-2.16	-2.16	-2.16	188.72	ND(LS)	NS(LS)
Multistage (1-degree)[c]	**2**	**4.10**	**0.13**	**1.75**	**-0.63**	**1.75**	**171.02**	**35.41**	**23.51**
Probit	2	6.55	0.04	2.16	-0.36	2.16	173.30	ND(LS)	NS(LS)

[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]Selected model.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.

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

Source: Auletta et al. 1998a

Table A-10. Model Predictions for Incidence of Urinary Bladder Hyperplasia in F_0 Female Rats Exposed to TnBP for 2 Years

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]: Dose below BMD	Scaled residuals[b]: Dose above BMD	Scaled residuals[b]: Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	1	0.11	0.74	0.12	-0.03	-0.26	124.28	47.67	28.56
Logistic	2	1.42	0.49	0.92	-0.09	0.92	123.59	73.30	59.41
LogLogistic[d]	1	0.09	0.76	0.09	-0.02	-0.24	124.27	47.03	28.66
LogProbit[d]	1	0.01	0.91	0.02	-0.01	-0.08	124.18	45.90	33.21
Multistage (1-degree)[e,]	2	4.00	0.14	-1.13	-1.17	-1.17	126.67	26.26	19.85
Multistage (2-degree)[e]	1	0.31	0.58	0.27	-0.04	-0.44	124.50	50.93	28.07
Multistage (3-degree)[e]	1	0.31	0.58	0.27	-0.04	-0.44	124.50	50.93	27.98
Probit[f]	**2**	**0.97**	**0.62**	**0.76**	**-0.10**	**0.76**	**123.14**	**65.64**	**53.59**
Weibull[c]	1	0.17	0.68	0.16	-0.03	-0.32	124.34	48.48	28.42

[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. All models provided adequate fit to the data. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

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

Source: Auletta et al. 1998a

As seen in Tables A-9 and A-10, and also in Table A-7, these values are higher than the $BMDL_{10}$ values obtained in the analyses of the incidences of urinary bladder hyperplasia reported in the intermediate-duration studies (Arnold et al. 1997; Tyl et al. 1997). As the data show, the incidences of urinary bladder hyperplasia at comparable high doses are higher in the intermediate-duration studies than in the chronic-duration study. A likely explanation for this phenomenon is provided in the chronic study by the observation that rats with malignant bladder tumors usually did not have any remaining uninvolved epithelium to evaluate for the presence or absence of hyperplasia (Auletta et al. 1998a). Whether urinary bladder hyperplasia is a potential precursor of urinary bladder tumors is not known for certain, but the data are suggestive. The lower incidence of hyperplasia at the higher dose levels in the chronic-duration study may just be the result of the hyperplasia transforming into neoplasia. As shown in Table A-7, dose levels that did not increase the incidence of urothelial hyperplasia in the intermediate-duration studies (NOAELs ranged from 9 to 15 mg/kg/day) also did not increase the incidence of urinary bladder hyperplasia in the chronic-duration study (NOAEL was 9 mg/kg/day) and did not increase the incidence of neoplastic lesions; thus, the NOAEL from intermediate-duration studies would also be protective for chronic exposure. Therefore, the intermediate-duration oral MRL of 0.08 mg/kg/day based on a $BMDL_{10}$ of 8.03 mg/kg/day is adopted also as chronic-duration oral MRL for TnBP.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(2-butoxyethyl) phosphate (TBEP)
CAS Numbers: 78-51-3
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 3
Species: Rat

Minimal Risk Level: 4.8 [X] mg/kg/day [ ] ppm

Reference: Monsanto Co. 1985b. Tributoxyethyl phosphate: Teratology study in rats with attachments and cover letter dated 083085. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. EPA96-910000298. OTS0528528.

Experimental design: Groups of female Sprague-Dawley rats (25/dose group) were administered 0, 250, 500, or 1500 mg TBEP/kg/day by gavage in corn oil on Gd 6–15. End points monitored included mortality, clinical signs, and body weight. The rats were euthanized on Gd 20. Immediately after kill, the uterus and ovaries were exposed and the number and location of viable and nonviable fetuses, early and late resorptions, and number of total implantations and corpora lutea were recorded. Fetuses were weighed, sexed, and examined for external malformations and variations. Fetuses were then prepared for visceral and skeletal examinations.

Effect noted in study and corresponding doses: There was one early death in the high-dose group, but the cause of death could not be determined. Chemical-related clinical signs included wet haircoat matting or staining with urine, brown material or blood on the face, neck, thorax, and/or anogenital area; this was observed in approximately half of the high-dose rats. Following dosing on Gd 6, two high-dose rats were ataxic, had reduced righting reflex, and/or were lethargic. Terminal body weight of the dams (unadjusted for uterine content) was significantly reduced, but only 6% relative to controls. Weight gain in high-dose rats was significantly reduced from Gd 6 on; during treatment (Gd 6–15), weight gain in this group was reduced 35%. Fetal body weight and sex ratios were not affected and neither were other developmental parameters. Treatment with TBEP did not affect the incidence of external, visceral, or skeletal anomalies. A maternal NOAEL and LOAEL of 500 and 1500 mg TBEP/kg/day, respectively, were defined in this study. The highest dose tested, 1500 mg/kg/day, was a developmental NOAEL based on no evidence of fetotoxicity or teratogenicity.

Dose and end point used for MRL derivation: BMDL of 477.25 mg/kg/day for decrease weight gain in pregnant rats on Gd 6–15.

[ ] NOAEL [ ] LOAEL [X] BMDL

Uncertainty Factors used in MRL derivation:

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

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

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.

Other additional studies or pertinent information that lend support to this MRL: Only one additional study was a potential source of data for MRL derivation. In that study, Sprague-Dawley rats (10/sex/dose level) were treated with up to 100 mg TBEP/kg/day by gavage in corn oil for 14 days (Komsta et al. 1989). End points monitored included clinical signs, body weight, hematology and clinical chemistry at termination, organ weights (brain, heart, liver, kidney, and spleen), microsomal liver enzyme activities, and gross and microscopic morphology of all major tissues and organs. The results did not show any significant differences between the treated and control groups for any of the parameters evaluated. However, because no adverse effects were reported, the Komsta et al. (1989) study was not considered a suitable basis for an MRL. An additional study that used considerably higher doses reported that 1 week after administration of a single gavage dose of ≥1,750 mg TBEP/kg, female rats showed slight tremors and piloerection, whereas those treated with 3,200 mg/kg exhibited tremors and abnormal gait; males appeared to be somewhat less sensitive. Examination of the sciatic nerve showed nerve degeneration in females dosed with ≥2,000 mg/kg. The NOAEL for males and females was 3,200 and 1,500 mg/kg, respectively.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF REDUCED WEIGHT GAIN IN PREGNANT RATS

Data from Monsanto Co. (1985b) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) were fit to the maternal body weight gain data to determine potential points of departure for the MRL (Table A-11). 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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body/organ weight or weight gain, in the absence of a clear criteria as to what level of change should be considered adverse, the BMR is defined as a change equal to 1 SD from the control mean (EPA 2000).

Table A-11. Data for the Change in Body Weight Gain in Pregnant Rats Exposed to TBEP on Gestation Days 6–15

Dose (mg/kg/day)	Number of animals tested	Body weight gain (g)	SD
0	25	55	5.5
250	25	53	8.4
500	25	52	7.6
1,500	25	36	11.1

Source: Monsanto Co. 1985b

As seen in Table A-12, using the criteria for model selection mentioned above, the Polynomial 3-degree polynomial model provided the best fit. The corresponding BMD_{1SD} was 824.97 mg/kg/day; the corresponding benchmark dose limit ($BMDL_{1SD}$) was 477.25 mg/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{1SD}$ of 477.25 mg/kg/day results in an acute-duration oral MRL of 4.8 mg/kg/day for TBEP. The model fit is shown in Figure A-5.

Table A-12. Model Predictions for Change in Maternal Body Weight Gain in Pregnant Rats Exposed to TBEP on Gestation Days 6–15

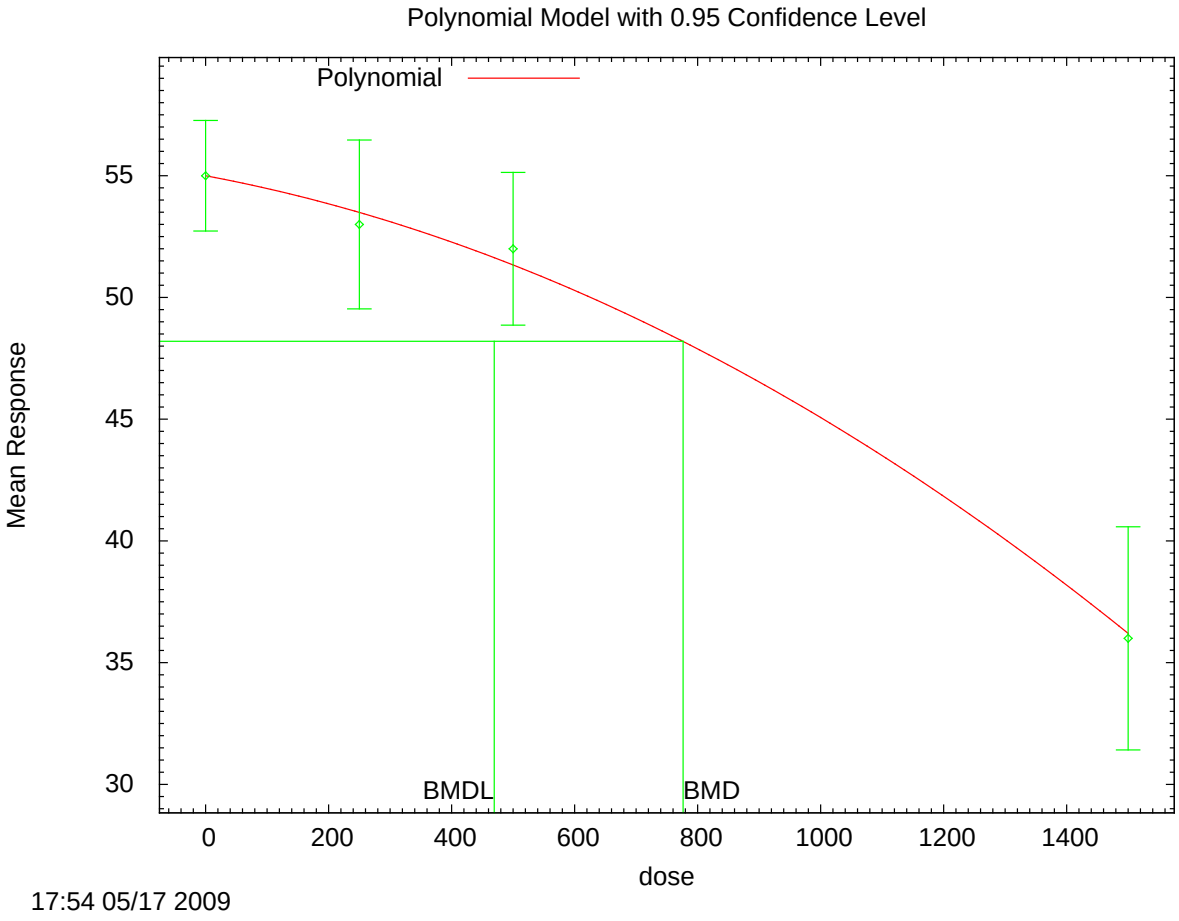
Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Constant variance									
Linear[d]	<0.0001	0.007	0.27	1.31	-0.43	1.31	530.01	635.60	521.84
Nonconstant variance									
Hill[e]	<0.0001	0.18	NA	0.47	-0.094	-0.47	525.61	766.47	NA
Linear[d]	<0.0001	0.18	0.27	1.37	-0.70	1.37	523.40	533.99	418.71
Polynomial (2-degree)[d]	<0.0001	0.18	0.42	0.44	-0.094	0.44	523.41	776.36	469.34
Polynomial (3-degree)[d,f]	**<0.0001**	**0.18**	**0.50**	**0.35**	**-0.07**	**0.35**	**523.23**	**824.97**	**477.25**
Power[e]	<0.0001	0.18	0.36	0.47	-0.094	0.47	523.60	766.71	461.90

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model did not fit variance data, but non-homogenous variance model did. With non-homogenous variance model applied, all models (except for the Hill model) provided adequate fit to means. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1 SD = change is 1 standard deviation from the control mean); BMR = benchmark response; NA = not applicable (p-value did not generate or BMDL computation failed)

Source: Monsanto Co. 1985b

Figure A-5. Fit of Polynomial Model (Nonconstant Variance) to Data on Body Weight Gain in Rats Exposed to TBEP on Gestation Days 6–15



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(2-butoxyethyl) phosphate (TBEP)
CAS Numbers: 78-51-3
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 9
Species: Rat

Minimal Risk Level: 0.09 [X] mg/kg/day [ ] ppm

Reference: Reyna MS, Thake DG. 1987a. Eighteen week feeding study of tributoxyethyl phosphate (TBEP) administered to Sprague-Dawley rats. Monsanto Agricultural Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0530087.

Experimental design: Groups of Sprague-Dawley rats (20/sex/group) were fed a diet containing 0, 300, 3,000, or 10,000 ppm TBEP for approximately 18 weeks (Reyna and Thake 1987a). This corresponds to doses of approximately 0, 17.3, 173, or 578 mg/kg/day for males and 0, 21, 209, or 698 mg/kg/day for females using food intake and body weight data from the study. End points monitored included clinical signs, body weight, food consumption, clinical chemistry and hematology (weeks 9 and 18), organ weights (brain, liver, kidneys, testes with epididymides), and gross and microscopic examination of all the major organs and tissues of controls and high-dose rats plus target tissues defined by the high-dose group and gross lesions from all necropsied animals.

Effect noted in study and corresponding doses: There were no treatment-related mortalities or adverse clinical signs. Body weight was not significantly affected by treatment with the test material. Food consumption was lower in high-dose males and females and mid-dose males during the first week of the study, but was comparable to controls the remainder of the study. Ophthalmological examinations at termination were unremarkable. Statistically significant hematological changes included decreased leukocyte (lymphocyte) in high-dose males on week 9, and increased platelet counts in high-dose males and females on week 9 and 18 and in mid-dose males on week 9. Significant clinical chemistry changes consisted of increased serum cholesterol in high-dose males on week 18 and on mid- and high-dose females on week 9, increased serum GGT activity in high-dose males on week 9 and 18 and in high-dose females on week 9, decreased serum cholinesterase in high-dose males and females on weeks 9 and 18, and decreased erythrocyte cholinesterase in all treated females only on week 9; brain cholinesterase activity was not affected. Absolute and relative liver weights were increased in high-dose males and females, but not significantly. Histopathological lesions were restricted to the liver of male rats and consisted of increased incidence of periportal hepatocellular hypertrophy (0/10, 0/10, 3/10, 7/10) and periportal vacuolization (1/10, 2/10, 6/10, 7/10).

Dose and end point used for MRL derivation: $BMDL_{10}$ of 8.88 mg/kg/day for hepatocyte vacuolization in male rats dosed in the diet for 18 weeks.

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

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes, ppm in food were converted to doses using mean food intake and body weight from the study.

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.

Other additional studies or pertinent information that lend support to this MRL: The study by Reyna and Thake (1987a) was the only intermediate-duration oral study that examined a wide range of end points available for review. In the same study, although presented separately, the investigators measured tail nerve conduction velocity at the end of the treatment period (Reyna and Thake 1987b). Following these measurements, the sciatic, tibial, and plantar nerves were processed for light microscopy. A significant reduction in nerve conduction velocity was measured only in high-dose females. Since both the absolute and relative refractory periods were decreased (the opposite of what would be expected in the case of a reduction in conduction velocity), the effect was not seen in males, and morphology of the nerves was unremarkable, the decrease in conduction velocity in females appeared questionable.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

APPENDIX A

BENCHMARK MODELING OF HEPATOCYTE HYPERTROPHY AND VACUOLIZATION IN MALE RATS

Incidence data for periportal hepatocyte hypertrophy and vacuolization in male rats exposed to TBEP (Reyna and Thake 1987a) were analyzed using the BMD approach for MRL derivation (Tables A-13 and A-14).

Table A-13. Incidence of Periportal Hepatocyte Hypertrophy in Male Rats Exposed to TBEP for 18 Weeks

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	10	0
17.3	10	0
173	10	3
578	10	7

Source: Reyna and Thake 1987a

Table A-14. Incidence of Periportal Hepatocyte Vacuolization in Male Rats Exposed to TBEP for 18 Weeks

Dose (mg/kg/day)	Total number of rats	Number of rats with lesions
0	10	1
17.3	10	2
173	10	6
578	10	7

Source: Reyna and Thake 1987a

Models in the EPA BMDS (version 2.1) were fit to the hepatocyte hypertrophy and hepatocyte vacuolation reported in male rats to determine a point 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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models.

Based on the criteria for model selection, comparing across models (Tables A-15 and A-16), the best fit for the hepatocyte hypertrophy data was provided by the Log Logistic model; the BMD_{10} and $BMDL_{10}$ were 80.62 and 21.92 mg TBEP/kg/day, respectively. The best fit for the incidence of hepatocyte vacuolization was provided also by the Log Logistic model, which estimated a BMD_{10} and $BMDL_{10}$ of 22.02 and 8.88 mg TBEP/kg/day, respectively. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 8.88 mg/kg/day results in an intermediate-duration oral MRL of 0.09 mg/kg/day for TBEP. The model fit for hepatocyte vacuolization is shown in Figure A-6.

Table A-15. Model Predictions for Incidence of Hepatocyte Hypertrophy in Male Rats Exposed to TBEP for 18 Weeks

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	2	0.28	0.87	-0.37	0.34	-0.37	28.85	78.52	32.71
Logistic	2	3.01	0.22	-0.77	1.33	1.33	32.18	168.20	104.90
LogLogistic[d,e]	**2**	**0.15**	**0.93**	**-0.31**	**0.20**	**-0.31**	**28.68**	**80.62**	**21.92**
LogProbit[d]	3	0.09	0.99	-0.13	0.20	-0.18	26.54	88.23	54.34
Multistage (1-degree)[f]	3	0.37	0.95	-0.59	0.05	-0.59	27.14	52.73	31.87
Multistage (2-degree)[f]	2	0.36	0.84	-0.54	0.26	-0.54	29.07	63.10	32.07
Probit	2	2.72	0.26	-0.70	1.30	1.30	31.71	156.18	100.50
Weibull[c]	2	0.31	0.86	-0.43	0.33	-0.43	28.92	74.28	32.50

[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. All models provided adequate fit to the data. Since the range of BMDLs was >3-fold, the model with lowest $BMDL_{10}$ was selected.
[f]Betas restricted to ≥0.

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

Source: Reyna and Thake 1987a

Table A-16. Model Predictions for Incidence of Hepatocyte Vacuolization in Male Rats Exposed to TBEP for 18 Weeks

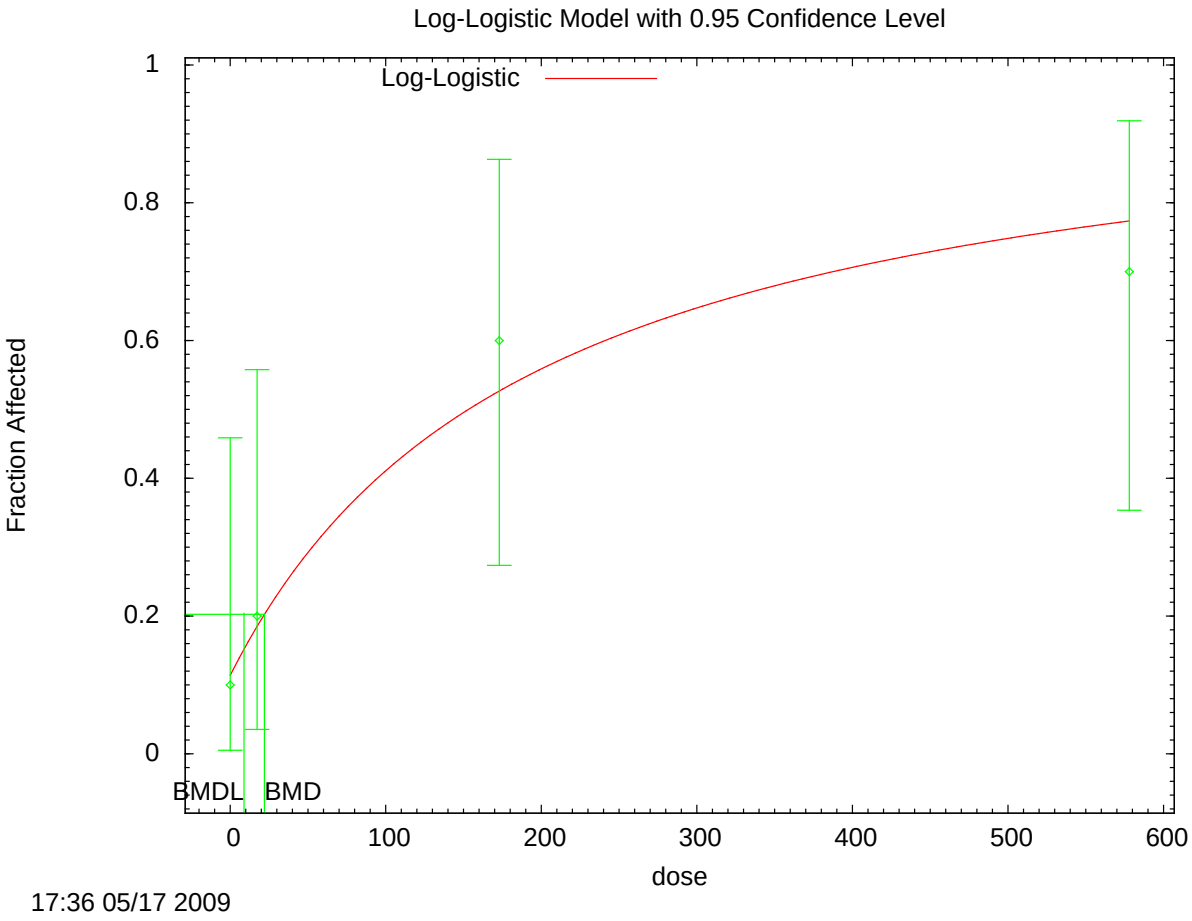
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Logistic	2	3.39	0.18	-0.27	1.48	1.48	49.64	95.80	60.25
LogLogistic[c]	**2**	**0.56**	**0.76**	**0.12**	**0.46**	**0.46**	**46.73**	**22.02**	**8.88**
LogProbit[d]	2	2.29	0.32	0.27	0.99	0.99	48.40	73.86	40.22
Multistage (1-degree)[e]	2	1.73	0.42	0.12	1.02	1.02	47.89	43.84	24.80
Probit	2	3.35	0.19	-0.24	1.50	1.50	49.59	93.91	62.31

[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]Selected model. All models provided adequate fit to the data. Since the range of BMDLs was >3-fold, the model with the lowest $BMDL_{10}$ was selected.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

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

Source: Reyna and Thake 1987a

Figure A-6. Fit of Log Logistic Model to Data on the Incidence of Periportal Hepatocyte Vacuolization in Male Rats Exposed to TBEP for 18 Weeks



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(1,3-dichloro-2-propyl) phosphate (TDCP)
CAS Numbers: 13674-87-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 4
Species: Rat

Minimal Risk Level: 0.05 [X] mg/kg/day [ ] ppm

Reference: Stauffer Chemical Co. 1981a. A two year oral toxicity/carcinogenicity study of fyrol FR-2 in rats. In: A two-year oral toxicity/carcinogenicity study of fyrol FR-2 in rats (volume I-IV) (final reports) with attachments, cover sheets and letter dated 093081. Stauffer Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. EPA88-8100282. OTS0204911.

Experimental design: Groups of Sprague-Dawley rats (60/sex/dose level) were fed a diet that provided 0, 5, 20, or 80 mg/kg/day of TDCP for 24 months. End points monitored included lethality, clinical signs, body weight, food consumption, hematology, clinical chemistry and urinalysis (at 3, 6, 12, 18, and 24 months, 9–10 rats/sex/sampling), gross necropsy, and histopathology at termination and at 12 months (10 rats/sex/dose).

Effect noted in study and corresponding doses: Mortality was comparable among groups during the first year of the study. Clinical signs were comparable among groups. Body weights were reduced in males and females 5–7% relative to controls at the 3- and 6-month time points. At week 50, mean body weight of males was 12% lower than controls, whereas mean body weight of females was 8% lower than controls. Hematology tests showed significant reductions in hemoglobin and hematocrit in high-dose males both at 3 and 6 months and of hemoglobin in females at 6 months. High-dose males also showed a reduction in red blood cell count at 6 months. The differences in mean hematological parameters between treated and control rats seen at 3 and 6 months were ≤5%. At 12 months, there were significant reductions in hemoglobin in high-dose males (10.6%) and females (7.5%) and in red cell counts in high-dose males (10.7%). None of these alterations were observed after 24 months of treatment with TDCP. Prothrombin times and partial thromboplastin times showed considerable variability from interval to interval and no consistent pattern of differences between treated and control rats were apparent during the study. Serum alkaline phosphatase levels were lower than controls in high-dose rats both at the 3- and 6-month intervals. BUN values in treated rats were not significantly different than in controls. Other clinical chemistry tests showed no consistent dose-related differences between controls and treated rats that could be attributed to treatment with TDCP. The most significant observations at 12 months were dose-related increases in absolute kidney and liver weights which achieved significance at the highest dose level; these changes in organs weight were not accompanied by histological alterations. Changes in kidney weight were more marked than those in liver weight, 48% increase in high-dose males and 39% increase in high-dose females relative to controls. At the lowest dose, kidney weight was increased 12% in males relative to controls. In mid-dose males, absolute thyroid and liver weight were increased by 14 and 12%, respectively; the corresponding increases in high-dose males were 25 and 26%. Since the kidney was the most sensitive end point in rats exposed to TDCP for 24 months in the same study, it would appear that the increase in kidney weight observed at 12 months is on the continuum of the same spectrum of health effects used to derive the chronic-duration MRL and may, in fact, be a precursor to the renal tubule hyperplasia seen in rats exposed to TDCP for 24 months. Since the hematological changes observed during the first year of the study are of questionable toxicological significance, it is appropriate

to use the changes in absolute kidney weight at the 12-month time point as basis for derivation of an intermediate-duration oral MRL for TDCP. Changes in absolute kidney weight in male and female rats were analyzed using the BMD approach for MRL derivation as detailed below.

Dose and end point used for MRL derivation: $BMDL_{1SD}$ of 4.69 mg/kg/day for increase absolute kidney weight in male rats.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{1SD}$

Uncertainty Factors used in MRL derivation:

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

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

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.

Other additional studies or pertinent information that lend support to this MRL: Only one addition intermediate-duration study is available for TDCP (Anonymous 1977). In that study, male rabbits were administered doses of 0, 2, 20, or 200 mg TDC/kg/day by gavage for 12 weeks. During the last week of treatment, male fertility was tested by mating the males with untreated females. Fertility was assessed by sacrificing the females at mid-gestation and evaluating their uteri. After the mating period, the males were euthanized and sperm from the cauda epididymides were analyzed for motility, morphology, and concentration. Blood was also collected for hematology and clinical chemistry tests. The pituitary, liver, kidneys, and reproductive tract were processed for microscopic examination. The treatment-related effects appeared to be a significant increase in relative liver weight (23%) and in absolute kidney weight (14%) at 200 mg/kg/day. Neither gross necropsy nor microscopic examinations revealed significant alterations in the organs examined.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF CHANGES IN KIDNEY WEIGHT IN RATS

Data from Stauffer Chem Co. (1981a) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) were fit to the absolute kidney weight male and female datasets (Tables A-17 and A-18) to determine potential points of departure for the MRL.

Table A-17. Data for the Change in Absolute Kidney Weight in Male Rats Exposed to TDCP for 1 Year

Dose (mg/kg/day)	Number of animals tested	Kidney weight (g)	Standard deviation
0	9	3.185	0.488
5	10	3.571	0.311
20	10	3.736	0.654
80	10	4.703	0.853

Source: Stauffer Chem Co. 1981a

Table A-18. Data for the Change in Absolute Kidney Weight in Female Rats Exposed to TDCP for 1 Year

Dose (mg/kg/day)	Number of animals tested	Kidney weight (g)	Standard deviation
0	10	2.031	0.193
5	10	2.179	0.198
20	10	2.271	0.269
80	10	2.836	0.443

Source: Stauffer Chem Co. 1981a

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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. For continuous data such as changes in body/organ weight or weight gain, in the absence of a clear criteria as to what level of change should be considered adverse, the BMR is defined as a change equal to 1 SD from the control mean (EPA 2000). Data from Stauffer Chemical Co. (1981a) were analyzed using the BMD approach for MRL derivation. BMD models in the EPA BMDS (version 2.1) were fit to the absolute kidney weight male and female datasets to determine potential points of departure for the MRL. For both data sets, constant variance models did not provide adequate fits (Tables A-19 and A-20). Selected non-constant variance models for male and female data predicted $BMDL_{1SD}$ values of 4.69 and 13.49 mg/kg/day, respectively; the lowest of these $BMDL_{1SD}$ was selected as the point of departure. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{1SD}$ of 4.69 mg/kg/day for increased kidney weights in male rats yields an intermediate-duration oral MRL of 0.05 mg/kg/day for TDCP. The model fit of the male data set is shown in Figure A-7.

Table A-19. Model Predictions for Change in Absolute Kidney Weight in Male Rats Exposed to TDCP for 1 Year

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Constant variance									
Linear[d]	<0.0001	0.02	0.52	0.21	-0.097	-0.86	3.98	34.6	25.79
Nonconstant variance									
Hill[e,f]	**<0.0001**	**0.11**	**0.48**	**0.98**	**-0.55**	**-0.98**	**1.70**	**13.36**	**4.69**
Linear[d]	<0.0001	0.11	0.48	0.24	-0.21	-1.06	0.67	24.86	16.31

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model did not fit variance data, but non-homogenous variance model did. With non-homogenous variance model applied, all models provided adequate fit to means. The constant variance model did not fit variance data, but the non-homogenous variance models did. With the non-homogenous variance model applied, two models provided adequate fit to means. The algorithms for the 2- and 3-degree polynomial and the Power models fit a linear model. Because range of $BMDL_{1SD}$ values from adequately fitting models was >3-fold, the model with the lowest $BMDL_{1SD}$ was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1 SD = change is 1 standard deviation from the control mean); BMR = benchmark response

Source: Stauffer Chem Co. 1981a

Table A-20. Model Predictions for Change in Absolute Kidney Weight in Female Rats Exposed to TDCP for 1 Year

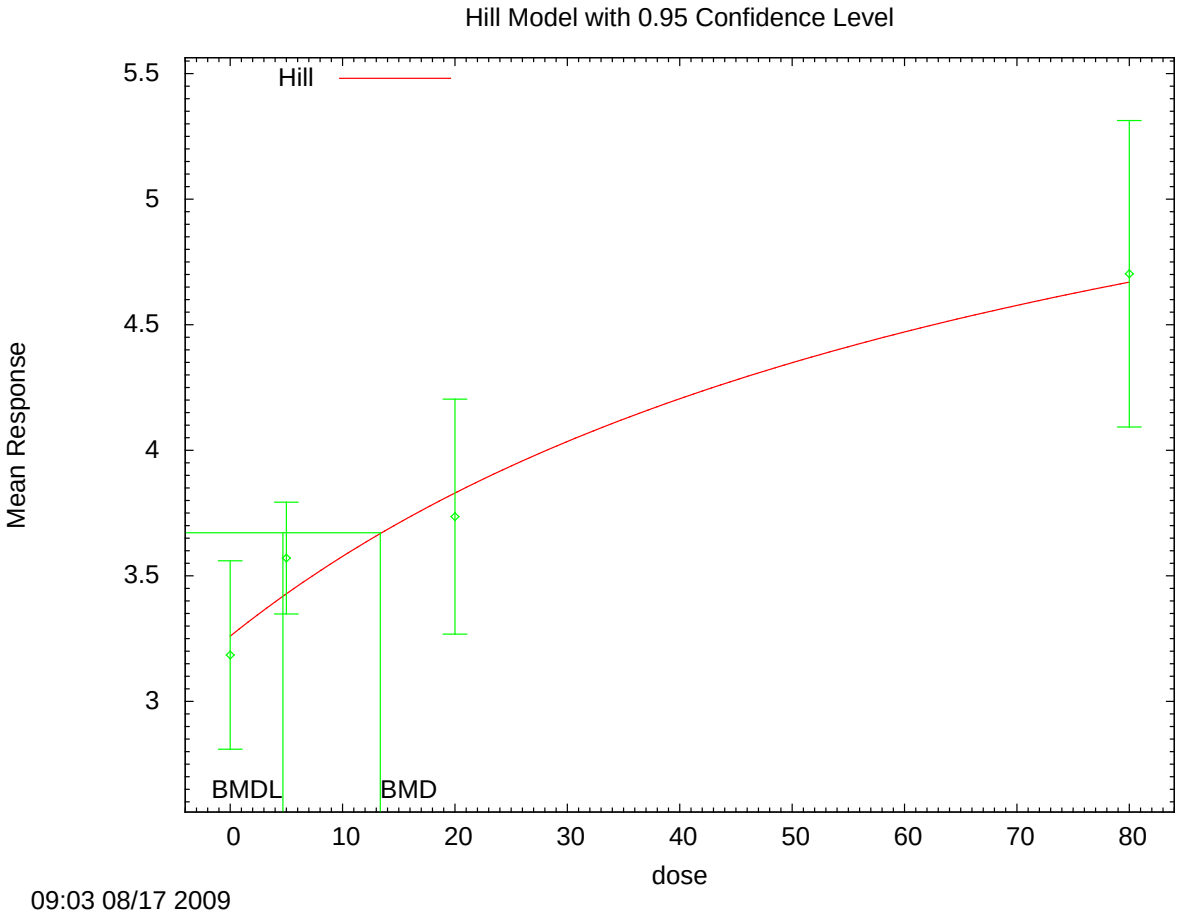
Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
Constant variance									
Linear[d]	<0.0001	0.02	0.72	0.012	-0.039	0.58	-55.58	29.59	22.67
Nonconstant variance									
Hill[e]	<0.0001	0.83	0.35	0.84	-0.42	0.84	-60.81	14.80	5.79
Linear[d,f]	**<0.0001**	**0.83**	**0.56**	**0.84**	**0.00092**	**0.84**	**-62.53**	**19.73**	**13.49**

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[d]Coefficients restricted to be negative.
[e]Power restricted to ≥1.
[f]Selected model. Constant variance model did not fit variance data, but non-homogenous variance model did. With non-homogenous variance model applied, all models provided adequate fit to means. The constant variance model did not fit variance data, but the non-homogenous variance model did. With the non-homogenous variance model applied, two models provided adequate fit to means The algorithms for the 2- and 3-degree polynomial and the Power models fit a linear model. Because range of $BMDL_{1SD}$ values from adequately fitting models was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., 1 SD = change is 1 standard deviation from the control mean); BMR = benchmark response

Source: Stauffer Chem Co. 1981a

Figure A-7. Fit of the Hill Model to Data on TDCP, Changes in Absolute Kidney Weight in Male Rats Exposed to TDCP for 1 Year



Source: Stauffer Chemical Co. 1981a

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tris(1,3-dichloro-2-propyl) phosphate (TDCP)
CAS Numbers: 13674-87-8
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 10
Species: Rat

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: Stauffer Chemical Co. 1981a. A two year oral toxicity/carcinogenicity study of fyrol FR-2 in rats. In: A two-year oral toxicity/carcinogenicity study of fyrol FR-2 in rats (volume I-IV) (final reports) with attachments, cover sheets and letter dated 093081. Stauffer Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. EPA88-8100282. OTS0204911.

Experimental design: Groups of Sprague-Dawley rats (60/sex/dose level) were fed a diet that provided 0, 5, 20, or 80 mg/kg/day of TDCP for 24 months. End points monitored included lethality, clinical signs, body weight, food consumption, hematology, clinical chemistry and urinalysis (periodically throughout the study), gross necropsy, and histopathology at termination and at 12 months (10 rats/sex/dose).

Effect noted in study and corresponding doses: Mortality was comparable among groups during the first year of the study, but increased in high-dose males during the second year and was significantly higher than controls at termination. Clinical signs were comparable among groups. Ophthalmological examinations at 18 and 24 months suggested that treatment with TDCP may have accelerated the development of sacculations along the course of the retinal arterioles in high-dose rats. In general, body weights of mid- and high-dose rats were lower than controls throughout the study. At termination, final body weights of high-dose males and females were 24 and 21% lower than controls, respectively. At week 50, body weights of mid-dose males and females were 12 and 8% lower than controls, respectively. There was no consistent pattern of differences among groups over time regarding food consumption. Hemoglobin, hematocrit, and total erythrocyte values were often significantly lower than controls in high-dose rats and the differences were usually more pronounced in males. This was observed throughout the study. At 24 months, prothrombin times and partial thromboplastin times were significantly elevated in high-dose males. Serum alkaline phosphatase values were lower than controls in high-dose males throughout the study; the biological significance of this is unclear. BUN was markedly elevated in a few mid- and high-dose rats at 18 and 24 months, which was consistent with microscopic evidence of renal pathology. Other clinical chemistry parameters were not consistently altered by treatment. Plasma cholinesterase was lower in high-dose females at 18 months (34%, significant) and 24 months (30%, not significant); changes at other times or in red blood cell cholinesterase were inconsistent. Urinalyses were unremarkable. Significant changes in organ weight consisted of increase absolute and relative liver, kidney, and thyroid weights in high-dose males and females at 12 and 24 months. At termination, gross observations revealed masses, nodules, and raised areas in the liver of high-dose rats; enlargement of the kidney in mid- and high-dose males and high-dose females plus higher incidence of discolorations, surface irregularities, masses, nodules, and cysts in treated rats than in controls; higher incidence of small seminal vesicles and testicular enlargement, masses, nodules, flaccidity, and discolorations in mid- and high-dose males. Nonneoplastic lesions that were significantly increased in treated rats were foci/areas of hepatocellular alterations (high-dose males and females), dilation of liver sinusoids (high-dose males and females), hyperplasia of convoluted tubular epithelium of the kidney (high-dose males and females, mid-dose males), and chronic nephropathy (high-dose males and females). None of these alterations were

seen at the 12-month interim kill. Hyperplasia of the renal convoluted tubular epithelium was the most sensitive effect and occurred with incidences of 2/45, 10/49, 28/48, and 24/46 in males as the doses increased; the corresponding incidences in females were 0/49, 1/48, 3/48, and 22/50. A NOAEL and LOAEL of 5 and 20 mg TDCP/kg/day, respectively, for renal epithelial hyperplasia in male rats was defined in this study.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 1.94 mg/kg/day for renal tubular epithelial hyperplasia in male rats dosed in the diet for 2 years.

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

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes, ppm in food were converted to doses by the investigators.

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.

Other additional studies or pertinent information that lend support to this MRL: The study by Stauffer Chemical Co. (1981a) was the only chronic-duration oral study available for review.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF RENAL TUBULE HYPERPLASIA IN RATS

Incidence data for renal tubule epithelial hyperplasia in male rats exposed to TDCP (Stauffer Chemical Co. 1981a) were analyzed using the BMD approach for MRL derivation (Table A-21).

Table A-21. Incidence of Renal Tubule Epithelial Hyperplasia in Rats Exposed to TDCP for 2 Years

Dose (mg/kg/day)	Total number of males	Males with lesions	Total number of females	Females with lesions
0	45	2	49	0
5	49	10	48	1
20	48	28	48	3
80	46	24	50	22

Source: Stauffer Chemical Co. 1981a

A glance at these incidences shows that males were clearly more sensitive than females. Therefore, the data set for hyperplasia of the renal convoluted tubular epithelium in males served as the basis for determining a point of departure for MRL derivation. Models in the EPA BMDS (version 2.1) were fit to the renal tubular epithelial hyperplasia data in male rats to determine potential points of departure for the MRL (Table A-22).

Table A-22. Model Predictions for Incidence of Renal Tubular Epithelial Hyperplasia in Male Rats

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	0	0.00	NA	0.00	0.00	0.00	137.16	3.04	1.95
Logistic	1	1.84	0.18	0.94	-0.18	-0.96	137.11	6.07	4.86
LogLogistic[d]	0	0.00	NA	0.00	0.00	0.00	137.16	3.22	1.46
LogProbit[d]	1	0.64	0.43	-0.26	0.62	0.62	135.78	4.40	3.35
Multistage (1-degree)[e,f]	**1**	**0.08**	**0.78**	**0.073**	**-0.23**	**-0.23**	**135.23**	**2.60**	**1.94**
Multistage (2-degree)[e]	0	0.00	NA	0.00	0.00	0.00	137.16	2.94	1.95
Probit	1	1.52	0.22	0.88	-0.19	0.88	136.74	5.59	4.53
Weibull[c]	0	0.00	NA	0.00	0.00	0.00	137.16	3.02	1.95

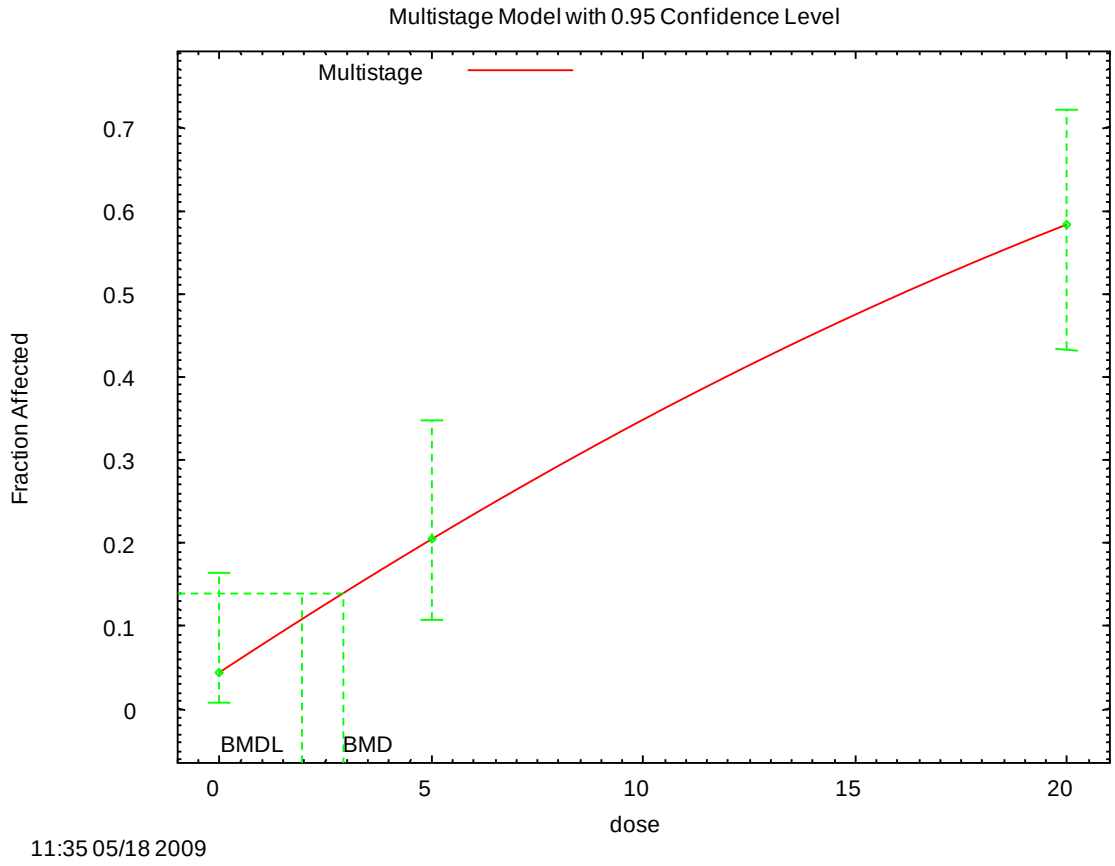
[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. No models provided adequate fit to the data with all doses, but adequate fits were achieved after dropping the highest dose. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected BMR; BMDL = 95% lower confidence limit on the BMD (subscripts denote BMR: i.e., $_{10}$ = dose associated with 10% extra risk); BMR = benchmark response; DF = degrees of freedom; NA = not applicable (p-value not generated)

Source: Stauffer Chem Co. 1981a

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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Since an adequate fit to the data set could not be obtained with any of the models, the high-dose was dropped, in accordance with EPA (2000) guidance. Comparing across models (Table A-22) using the selection criteria mentioned above shows that the Multistage (1-degree polynomial) model provided the best fit to the renal epithelial hyperplasia. From this model, the predicted dose associated with a 10% extra risk (BMD_{10}) was 2.60 mg TDCP/kg/day and the ($BMDL_{10}$ was 1.94 mg TDCP/kg/day. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 1.94 mg/kg/day yields a chronic-duration oral MRL of 0.02 mg/kg/day for TDCP. The model fit is shown in Figure A-8.

Figure A-8. Fit of Multistage (1-Degree Polynomial) Model to Incidence of Renal Tubular Epithelia Hyperplasia in Male Rats Exposed to TDCP for 2 Years



Source: Stauffer Chemical Co. 1981a

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tricresyl phosphate (TCP)
CAS Numbers: 1330-78-5
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 53
Species: Rat

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

Reference: NTP. 1994. Toxicology and carcinogenesis studies of tricresyl phosphate (CAS No. 1330-78-5) in F344/N rats and B6C3F$_1$ mice (gavage and feed studies). Program NT. TR 433.

Experimental design: Groups of Fischer-344 rats (95/sex/dose) were fed a diet containing 0 (control), 75, 150, or 300 ppm TCP for 104 weeks. This diet supplied doses of 0, 3, 6, or 13 mg TCP/kg/day to males and 0, 4, 7, or 15 mg/kg/day to females (estimated by the investigators). The TCP used in the NTP studies was a mixed isomer preparation of 79% tricresyl phosphate esters consisting of 21% tri-*m*-cresyl phosphate, 4% tri-*p*-cresyl phosphate, <1% tri-*o*-cresyl phosphate, and other unidentified tricresyl phosphate esters. Fifteen rats per sex per dose group were euthanized after 3, 9, and 15 months of the diet. Additional 95 rats per sex were fed a diet with 600 ppm TCP (dose not provided) for 22 weeks and then were place on the control diet; of these, thirty rats per sex were examined at 9 and 15 months. Ten rats per sex in the 600 ppm group were also euthanized at 3 months. All rats were observed twice daily. Clinical findings and body weight were recorded weekly for 13 weeks, then monthly and at the interim evaluations. Food consumption was measured once per month. Neurobehavioral assessments were conducted before exposure and at 3, 9, and 15 months (forelimb and hindlimb grip strength). Blood was collected at 3, 9, and 15 months for hematology tests and serum cholinesterase activity. At interim kills the adrenal, brain, kidney, liver, and testes were weighted. All rats were necropsied and a complete histopathologic examination was conducted in all rats.

Effects noted in study and corresponding doses: Survival was not significantly affected by exposure to TCP. Mean body weight was comparable among groups throughout the study. Food consumption was not significantly affected. There were no chemical-related clinical signs. The only significant alteration in organ weight was an increase in absolute (25%) and relative (23%) weight of the left adrenal in females at the 3 month interval at 15 mg/kg/day; the corresponding increases in adrenal weight in the 600 ppm females were 37% and 38%. There were no significant chemical-related changes in hematological values. Serum cholinesterase was reduced at the 3, 9, and 15 month interval, more severely in females (23% at 7 mg/kg at 3 months, 35% at 7 mg/kg at 9 months; 32% at 4 mg/kg at 15 months). Results of the neurological tests showed a significant reduction (11%) in hindlimb grip strength in male rats dosed with 13 mg/kg/day at the 3 month evaluation. Chemical-related non-neoplastic lesions were restricted to the adrenal cortex of both sexes and the ovary of females. Cytoplasmic vacuolization of the adrenal gland occurred in males only at the 3 months examination in the 600 ppm group (10/10 vs 0/10 in other groups). In females, incidences were significantly elevated at all intervals examined except in the 600 ppm group beyond 3 months, suggesting reversibility of the lesion if treatment ceased. At 3 months the incidences were 0/10, 0/10, 1/10, 10/10 and 9/10 in the 0, 75, 150, 300, and 600 ppm groups, respectively; in the same groups, at 9 months the incidences were 1/10, 0/10, 3/10, 10/10, and 0/10. The lesion was characterized by increased number of small, fine vacuoles in the cortical cells of the zona fasciculata resulting in a ground glass appearance and an increase in cell size. Minimal to mild interstitial cell hyperplasia in the ovaries occurred at 3 months in females dosed 7 and 15 mg/kg/day (0/10, 0/10, 6/10,

10/10, and 10/10 in the 0, 75, 150, 300, and 600 ppm groups, respectively). However, the incidence of ovarian lesions in the 600 ppm group at the 9-month evaluation (this group terminated exposure at 22 weeks) was only 40% (4/10), again suggesting reversibility once treatment ceased. The lesion was characterized by an increase in size and possibly number of interstitial cells without any particular alteration of ovarian architecture. No significant lesions were found in other tissues.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 3.72 mg/kg/day for ovarian lesions in female rats.

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

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were estimated by the investigators based on body weight and food consumption 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? No.

Other additional studies or pertinent information that lend support to this MRL: Adrenal gland and ovarian lesions were also reported in other intermediate-duration studies in rats such as the 13-week gavage and dietary studies conducted by NTP (1994) and studies conducted by Latendresse and coworkers (Latendresse et al. 1993, 1994b). However, these studies used relatively high doses of TCP. In addition, Latendresse et al. (1993, 1994b) used a single dose level of 400 mg TCP/kg/day, whereas the NTP (1994) 13-week studies used doses ranging from 50 to 800 mg TCP/kg/day. In the 2-year NTP (1994) study in mice, adrenal lesions were seen in all groups of male and female mice, including controls, with an incidence near or at 100% at 9, 15, and 24 months (NTP 1994). At the 3-month interim kill, only high-dose male mice (27 mg TCP/kg/day) showed a significant increase (6/10) relative to controls (0/8).

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF ADRENAL AND OVARIAN LESIONS IN RATS

Incidences of adrenal and ovarian lesions in rats at the 3- and 9-month interim kills are presented in Table A-23.

Table A-23. Incidences of Adrenal Cortex and Ovarian Lesions in Female F344 Rats Exposed to TCP for 3 or 9 Months

Incidence of cytoplasmic vacuolization of the adrenal cortex				
Dose (mg/kg/day)	0	4	7	15
At 3 months	0/10	0/10	1/10	10/10
At 9 months	0/10	0/10	3/10	10/10
Incidence of hyperplasia of the interstitial ovarian cells				
At 3 months	0/10	0/10	6/10	10/10
At 9 months	0/10	0/10	1/10	10/10

Source: NTP 1994

Incidence data for cytoplasmic vacuolization of the adrenal cortex in female rats and of hyperplasia of the interstitial ovarian cell in female rats exposed to TCP (NTP 1994) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) were fit to the adrenal and ovarian lesion 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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Using these criteria, the best fitting model for each of the four data sets were selected and the results are summarized in Table A-24.

Table A-24. Summary of Modeling of Intermediate-Duration Data for Tricresyl Phosphate in Female Rats

	Best fitting model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Adrenal lesions at 3 months	LogLogistic	7.00	5.69
Adrenal lesions at 9 months	LogLogistic	6.49	4.58
Ovarian lesions at 3 months	**Weibull**	**6.21**	**3.72**
Ovarian lesions at 9 months	LogLogistic	7.00	5.69

As shown in Table A-24, among the models selected as providing the best fit for each of the four data sets, the lowest $BMDL_{10}$ value is 3.72 mg TCP/kg/day and was obtained with the fit of the Weibull model for increased incidence of hyperplasia of the interstitial ovarian cells at the 3-month time point. To be protective of human health, this value is used as point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 3.72 mg TCP/kg/day results in an intermediate-duration oral MRLs of 0.04 mg/kg/day for TCP. Further details of the modeling of this data set are shown in Table A-25. The model fit of the data is shown in Figure A-9. It should be noted that the Multistage (2-degree) model, that provided a lower

$BMDL_{10}$ of 1.53 mg/kg/day, was not considered the best fitting model because it has relatively high residuals and the highest AIC and lowest goodness-of-fit p-value among the models that fit the data.

Table A-25. Model Predictions for Incidence of Hyperplasia of the Interstitial Cells in the Ovary of Female F344 Rats Fed TCP in the Diet for 3 Months

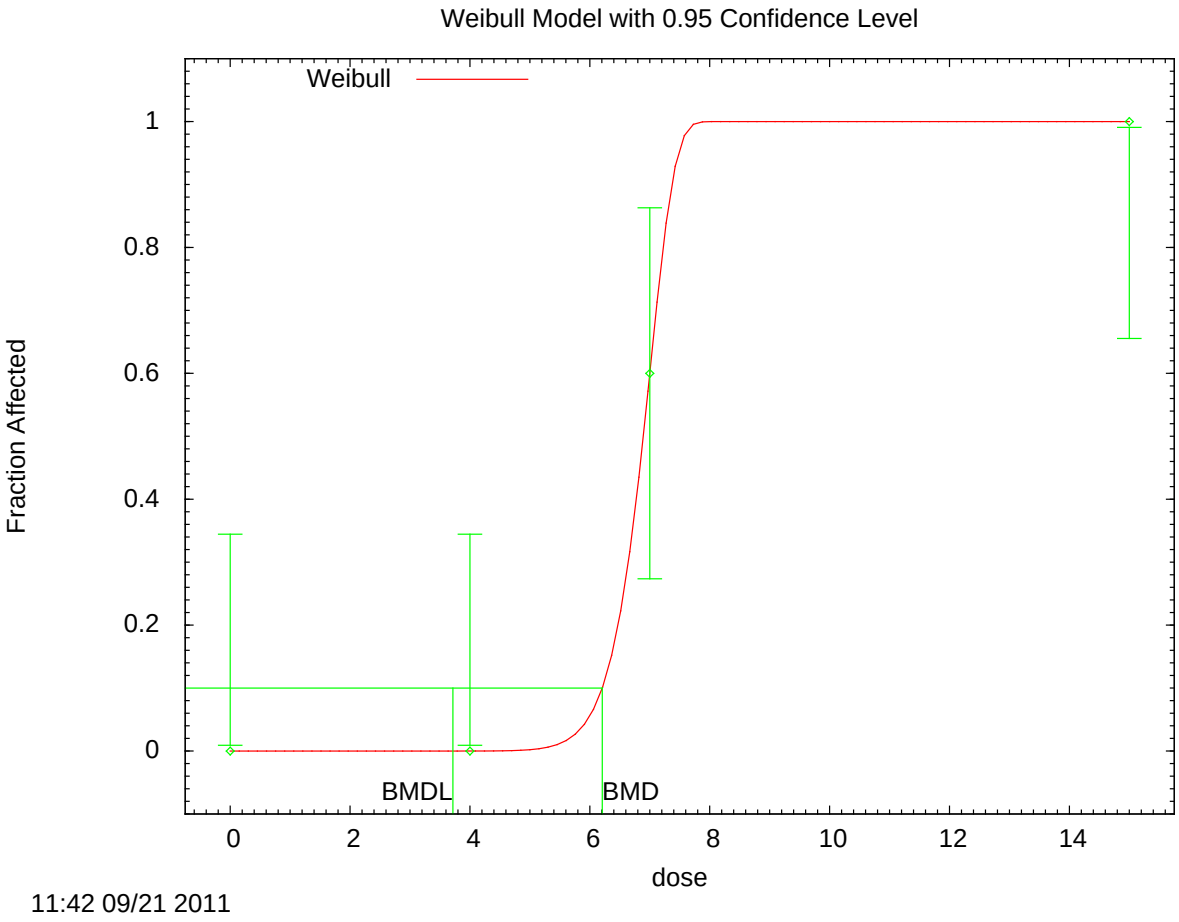
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	3	0.26	0.97	-0.48	0.18	-0.48	15.95	4.87	3.62
Logistic	2	0.00	1.00	0.00	0.00	0.00	17.46	6.59	3.80
LogLogistic[d]	3	0.00	1.00	-0.03	0.00	-0.03	15.46	6.06	3.91
LogProbit[d]	2	0.00	1.00	0.00	0.00	0.00	17.46	6.06	3.86
Multistage (1-degree)[e]	3	8.08	0.04	0.00	-2.40	-2.40	28.67	ND(LS)	ND(LS)
Multistage (2-degree)[e]	3	3.32	0.34	0.00	-1.64	-1.64	21.21	2.66	1.53
Multistage (3-degree)[e]	3	1.76	0.62	0.00	-1.19	-1.19	18.47	3.70	2.01
Probit	2	0.00	1.00	0.00	0.00	0.00	17.46	6.22	3.73
Weibull[c,f]	**3**	**0.00**	**1.00**	**-0.02**	**0.00**	**-0.02**	**15.46**	**6.21**	**3.72**

[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. All models (except the Multistage 1-degree) provided an adequate fit of the data. Since the range of BMDLs was <3-fold, the model with the lowest AIC was selected.

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

Source: NTP 1994

Figure A-9. Fit of Weibull Model to Incidence of Hyperplasia of Ovarian Interstitial Cells in Female Rats Exposed to TCP for 3 Months



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Tricresyl phosphate (TCP)
CAS Numbers: 1330-78-5
Date: September 2012
Profile Status: Draft 3, Post-public
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [] Intermediate [X] Chronic
Graph Key: 69
Species: Rat

Minimal Risk Level: 0.02 [X] mg/kg/day [ ] ppm

Reference: NTP. 1994. Toxicology and carcinogenesis studies of tricresyl phosphate (CAS No. 1330-78-5) in F344/N rats and B6C3F$_1$ mice (gavage and feed studies). Program NT. TR 433.

Experimental design: Groups of Fischer-344 rats (95/sex/dose) were fed a diet containing 0 (control), 75, 150, or 300 ppm TCP for 104 weeks. This diet supplied doses of 0, 3, 6, or 13 mg TCP/kg/day to males and 0, 4, 7, or 15 mg/kg/day to females (estimated by the investigators). Fifteen rats per sex per dose group were euthanized after 3, 9, and 15 months of the diet. Additional 95 rats per sex were fed a diet with 600 ppm TCP (dose not provided) for 22 weeks and then were place on the control diet; of these, thirty rats per sex were examined at 9 and 15 months. Ten rats per sex in the 600 ppm group were also euthanized at 3 months. All rats were observed twice daily. Clinical findings and body weight were recorded weekly for 13 weeks, then monthly and at the interim evaluations. Food consumption was measured once per month. Neurobehavioral assessments were conducted before exposure and at 3, 9, and 15 months (forelimb and hindlimb grip strength). Blood was collected at 3, 9, and 15 months for hematology tests and serum cholinesterase activity. At interim kills the adrenal, brain, kidney, liver, and testes were weighted. All rats were necropsied and a complete histopathologic examination was conducted in all rats.

Groups of B6C3F$_1$ mice (95/sex/group) were fed a diet containing 0, 75, 150, or 300 ppm TCP for 104 weeks. This diet supplied doses of 0, 7, 13, or 27 mg TCP/kg/day to males and 0, 8, 18, or 37 mg/kg/day to females. Fifteen mice per sex per group were euthanized after 3, 9, and 15 months of the diet. All mice were observed twice daily. Clinical findings and body weight were recorded weekly for 13 weeks, then monthly and at the interim evaluations. Food consumption was measured once per month. Feed consumption was measured once per month. Neurobehavioral assessments were conducted before exposure and at 3, 9, and 15 months (forelimb and hindlimb grip strength). Blood was collected at 3, 9, and 15 months for hematology tests and serum cholinesterase activity. At interim kills the adrenal, brain, kidney, liver, and testes were weighted. All mice were necropsied and subjected to a complete histopathologic examination.

Effect noted in study and corresponding doses: Survival of rats was not significantly affected by exposure to TCP. Mean body weight was comparable among groups throughout the study. Food consumption was not significantly affected. There were no chemical-related clinical signs. The only significant alteration in organ weight was an increase in absolute (25%) and relative (23%) weight of the left adrenal in females at the 3 month interval at 15 mg/kg/day; the corresponding increases in adrenal weight in the 600 ppm females were 37% and 38%. There were no significant chemical-related changes in hematological values. Serum cholinesterase was reduced at the 3, 9, and 15 month interval, more severily in females (23% at 7 mg/kg at 3 months, 35% at 7 mg/kg at 9 months; 32% at 4 mg/kg at 15 months). Results of the neurological tests showed a significant reduction (11%) in hindlimb grip strength in male rats dosed with 13 mg/kg/day at the 3 month evaluation. Chemical-related non-

neoplastic lesions were restricted to the adrenal cortex of both sexes and the ovary of females. Cytoplasmic vacuolization of the adrenal gland occurred in males only at the 3 months examination in the 600 ppm group (10/10 vs 0/10 in other groups). In females, incidences were significantly elevated at all intervals examined except in the 600 ppm group beyond 3 months, suggesting reversibility of the lesion if treatment ceased. At 3 months the incidences were 0/10, 0/10, 1/10, 10/10 and 9/10 in the 0, 75, 150, 300, and 600 ppm groups, respectively; in the same groups, at 9 months the incidences were 1/10, 0/10, 3/10, 10/10, and 0/10. The lesion was characterized by increased number of small, fine vacuoles in the cortical cells of the zona fasciculata resulting in a ground glass appearance and an increase in cell size. Minimal to mild interstitial cell hyperplasia in the ovaries occurred at 3 months in females dosed 7 and 15 mg/kg/day (0/10, 0/10, 6/10, 10/10, and 10/10 in the 0, 75, 150, 300, and 600 ppm groups, respectively). However, the incidence of ovarian lesions in the 600 ppm group at the 9-month evaluation (this group terminated exposure at 22 weeks) was only 40% (4/10), again suggesting reversibility once treatment ceased. The lesion was characterized by an increase in size and possibly number of interstitial cells without any particular alteration of ovarian architecture. No significant lesions were found in other tissues.

Survival of mice was not significantly affected by exposure to TCP. Mean body weight was comparable among groups throughout the study. Food consumption was not significantly affected. There were no chemical-related clinical signs. There were no significant chemical-related changes in hematological values. Serum cholinesterase values were significantly reduced in all treated groups (20–35% with the low dose). The only significant neurological effect was a reduction (7%) of hindlimb grip strength in high-dose females at the 3-month interim examination. Significant alterations in organ weight were limited to the adrenal glands and consisted in a decrease in absolute weight in high-dose males (33%) and increase (40%) in high-dose females, both at the 15-month evaluation. Histopathology was limited to the adrenal gland and liver. High-dose males had a significant increased incidence of ceroid pigmentation in the gland (0/8, 3/10, 3/30, 6/10) at the 3-month examination. At 2 years almost all mice had ceroid pigmentation but the severity increased with dose. The lesion consisted of macrophages and/or epithelial cells in various stages of distension from the accumulation of yellow-brown cytoplasmic pigment. Male mice from the mid- and high-dose groups had significantly elevated incidences of clear cell focus (5/52, 8/49, 17/49, 12/50), fatty change (6/52, 10/49, 23/49, 22/50), and ceroid pigmentation (0/52, 0/49, 30/49, 28/50) in the liver at termination (2 years). Cells within foci were enlarged and contained one or more medium to large clear spaces in the cytoplasm. The fatty change consisted of small vacuoles in individual hepatocytes, randomly distributed throughout the liver; the severity was never greater than moderate. Ceroid pigmentation consisted of cells containing fine, yellow-brown granules in their cytoplasm. There were no significant histological alterations in other organs.

Dose and end point used for MRL derivation: $BMDL_{10}$ of 2.12 mg/kg/day for ovarian lesions in female rats.

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

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were estimated by the investigators based on body weight and food consumption 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? No.

Other additional studies or pertinent information that lend support to this MRL: Adrenal gland and ovarian lesions were also reported in other intermediate-duration studies in rats such as the 13-week gavage and dietary studies conducted by NTP (1994) and studies conducted by Latendresse and coworkers (Latendresse et al. 1993, 1994b). However, these studies used relatively high doses. In addition, Latendresse et al. (1993, 1994b) used a single dose level of 400 mg TCP/kg/day, whereas the NTP (1994) 13-week studies used doses ranging from 50 to 800 mg TCP/kg/day.

Agency Contacts (Chemical Managers): G. Daniel Todd, Ph.D.

BENCHMARK MODELING OF ADRENAL AND OVARIAN LESIONS IN RATS AND LIVER LESIONS IN MICE

Incidences of adrenal and ovarian lesions in rats and liver lesions in mice at the 15-month and 2-year interim kills are presented in Table A-26.

Table A-26. Adrenal Cortex and Ovarian Lesions in Female F344 Rats and Liver Lesions in B6C3F$_1$ Male Mice Exposed to TCP

Incidence of cytoplasmic vacuolization of the adrenal cortex in rats				
Dose (mg/kg/day)	0	4	7	15
At 15 months	0/9	0/8	0/10	10/10
At 2 years	14/51	12/53	16/50	36/50
Incidence of hyperplasia of the interstitial ovarian cells in rats				
At 15 months	0/9	0/8	3/10	9/10
At 2 years	0/51	0/53	0/50	15/50
Incidence of liver lesions in mice after 2 years				
Dose (mg/kg/day)	0	7	13	27
Clear cell foci	5/52	8/49	17/49	12/50
Fatty change	6/52	10/49	23/49	22/50
Ceroid pigmentation	0/52	0/49	30/49	28/50

Incidence data for cytoplasmic vacuolization of the adrenal cortex and of hyperplasia of the interstitial ovarian cell in female rats and of liver lesions in male mice exposed to TCP (NTP 1994) were analyzed using the BMD approach for MRL derivation. Models in the EPA BMDS (version 2.1.1) were fit to the adrenal and ovarian lesion 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 the models providing adequate fit to the data, the lowest benchmark dose (BMDL, the lower limit of a one-sided 95% confidence interval on the BMD) is selected as the point of departure when differences between the BMDLs estimated from these models are >3-fold; otherwise, the BMDL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, BMDs and BMDLs associated with an extra risk of 10% are calculated for all models. Using these criteria, the best fitting model for each of the four data sets were selected and the results are summarized in Table A-27.

Table A-27. Summary of Modeling of Chronic-Duration Data for Tricresyl Phosphate

		Best fitting model	BMD_{10} (mg/kg/day)	$BMDL_{10}$ (mg/kg/day)
Adrenal lesions at 15 months (rats)		Weibull	11.44	6.73
Adrenal lesions at 2 years (rats)		Multistage 3-degree	7.11	3.73
Ovarian lesions at 15 months (rats)		**Multistage 3-degree**	**5.22**	**2.12**
Ovarian lesions at 2 years (rats)		LogLogistic	13.92	10.37
Liver lesions at 2 years (mice)	Clear foci	Multistage 2-degree	7.46	3.25
	Fatty change	LogLogistic	3.91	2.59
	Ceroid pigmentation	LogLogistic	11.22	8.64

As shown in Table A-27, among the models selected as providing the best fit for each of the four data sets, the lowest $BMDL_{10}$ value is 2.12 mg TCP/kg/day and was obtained with the fit of the Multistage 3-degree model for increased incidence of hyperplasia of the interstitial ovarian cells at the 15-month time point. To be protective of human health, this value is used as point of departure for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the $BMDL_{10}$ of 2.12 mg TCP/kg/day results in a chronic-duration oral MRL of 0.02 mg/kg/day for TCP. Further details of the modeling of this data set are shown in Table A-28. The model fit of the data is shown in Figure A-10.

Table A-28. Model Predictions for Incidence of Hyperplasia of the Interstitial Cells in the Ovary of Female F344 Rats Fed TCP in the Diet for 15 Months

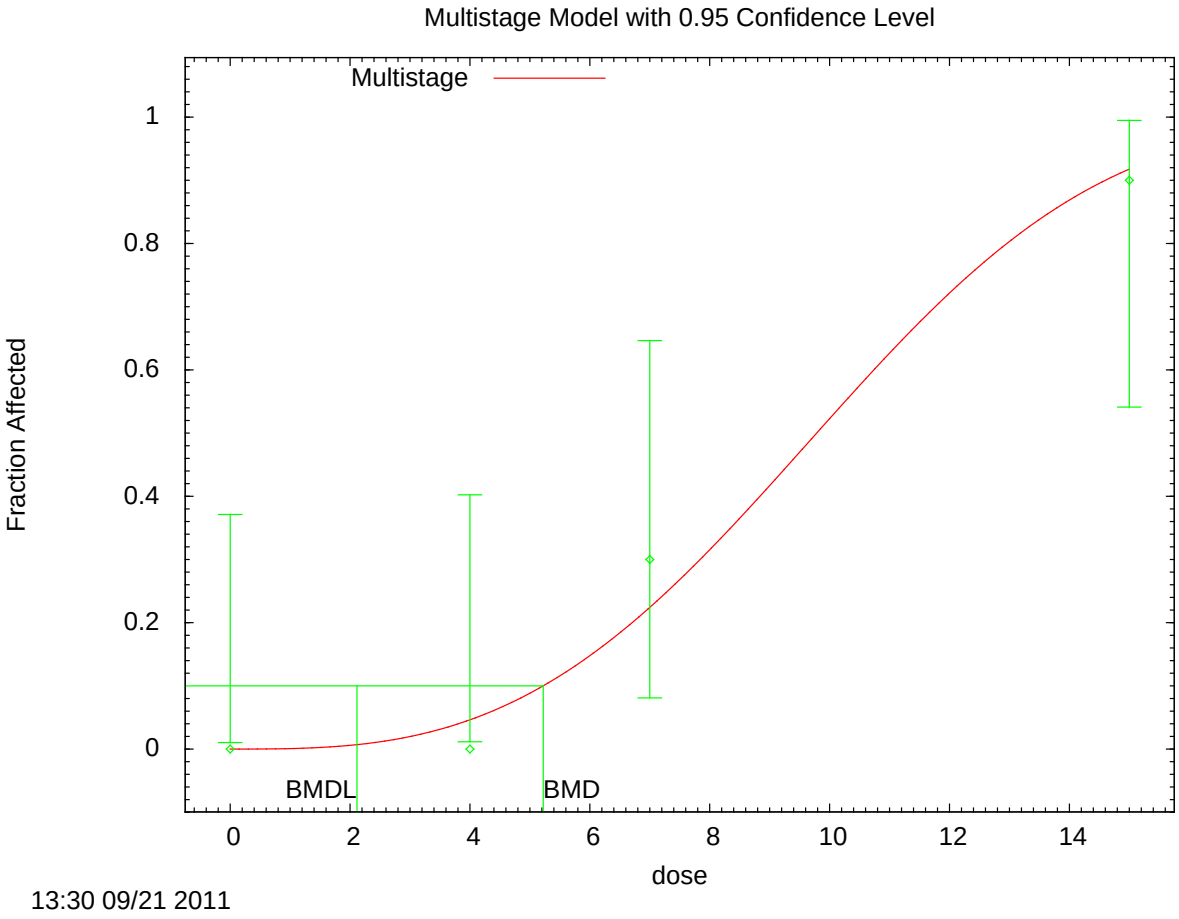
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]: Dose below BMD	Scaled residuals[b]: Dose above BMD	Scaled residuals[b]: Overall largest	AIC	BMD_{10} (mg/kg-day)	$BMDL_{10}$ (mg/kg-day)
Gamma[c]	2	0.41	0.81	-0.49	0.37	-0.49	23.35	5.37	3.22
Logistic	2	1.13	0.57	-0.73	0.65	-0.73	24.39	5.29	3.31
LogLogistic[d]	2	0.34	0.84	-0.48	0.28	-0.48	23.28	5.41	3.46
LogProbit[d]	2	0.24	0.89	-0.38	0.27	-0.38	23.10	5.47	3.61
Multistage (1-degree)[e]	3	5.59	0.13	0.00	-1.67	-1.67	28.84	1.41	0.89
Multistage (2-degree)[e]	3	1.42	0.70	0.00	-1.05	-1.05	23.14	3.61	1.96
Multistage (3-degree)[e,f]	**3**	**0.76**	**0.86**	**-0.62**	**0.58**	**-0.62**	**21.82**	**5.22**	**2.12**
Probit	2	0.96	0.62	-0.68	0.64	-0.68	24.10	5.25	3.18
Weibull[c]	2	0.69	0.71	-0.66	0.48	-0.66	23.81	5.07	2.79

[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. All models provided an adequate fit of the data. The range of $BMDL_{10}$ values from adequately fitting models was >3-fold mainly due to the poor fitting of the Multistage 1-degree model (highest AIC value, largest scaled residuals, and worst goodness-of-fit p-value). $BMDL_{10}$ values from the remaining models were <3-fold, thus; the model with the lowest AIC value was selected (Multistage 3-degree).

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

Source: NTP 1994

Figure A-10. Fit of Multistage 3-Degree Polynomial Model to Incidence of Hyperplasia of the Interstitial Cells in the Ovary of Female F344 Rats Fed TCP in the Diet for 15 Months



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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 nontechnical 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 judgment, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment 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

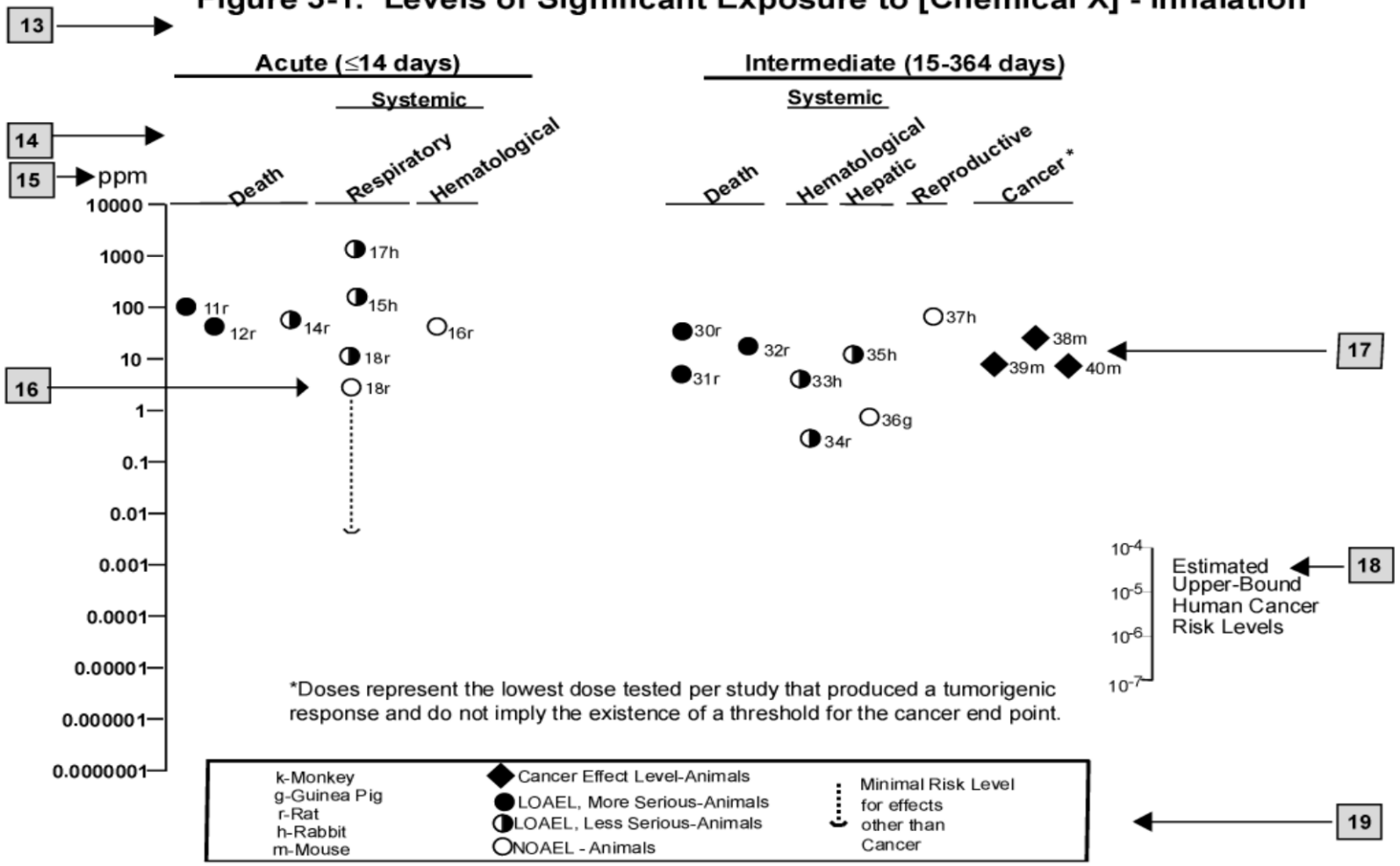
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 → [a] The number corresponds to entries in Figure 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/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
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