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, 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30333.

Acute-, intermediate-, and chronic-duration oral MRLs were derived for acrylamide using the PBPK model described by Sweeney et al. (2010). The PBPK model was used to estimate rat internal dose metrics for blood acrylamide and glycidamide (a readily-formed metabolite of acrylamide in aqueous environment) for each of the administered acrylamide dose levels in the principal study and for estimating HEDs. Code for acrylamide and glycidamide rat and human PBPK models was provided by L.M. Sweeney along with data used to evaluate model performance and documentation of parameter values reported in Sweeney et al. (2010). Refer to Section 3.4.5 for a detailed description of the PBPK model of Sweeney et al. (2010).

The internal dose metric selected for interspecies dosimetry extrapolation was the time-weighted average (TWA) concentration of either acrylamide or glycidamide. A time-integrated dose metric (e.g., TWA) was selected based, in part, on mechanistic considerations. The extent to which acrylamide and glycidamide contribute to toxicity observed following ingestion exposures to acrylamide is not known with certainty. There is evidence to suggest that epoxide metabolites of acrylamide contribute to germ cell mutations in male mice (Ghanayem et al. 2005a). Given the uncertainty in the relative importance of

acrylamide and glycidamide in producing toxicity, the conservative assumption was made that toxic response would be related to a time-integrated function of blood acrylamide concentration (e.g., TWA). This assumption resulted in the lowest HED and MRL based on male rat reproductive effects.

There is evidence to suggest that some of the neurological effects observed in animals can be elicited by administration of acrylamide or its epoxide metabolite (glycidamide). However, in one study of male rats acrylamide (25 or 50 mg/kg/day) or glycidamide (50 or 100 mg/kg/day) administered via intraperitoneal injection for 8 days, only acrylamide elicited poor performance on the hindlimb splay test (Costa et al. 1995). Given the uncertainty in the relative importance of acrylamide and glycidamide in producing toxicity, the conservative assumption was made that toxic response would be related to a time-integrated function of blood acrylamide concentration (e.g., TWA). This assumption resulted in the lowest HEDs and MRLs based on neurotoxicity in rats.

TWA concentrations of acrylamide and glycidamide in mixed venous blood were calculated as follows:

$$TWA = \left(\int_{t=0}^{t=i} C_{Blood} \right) \div t_i$$

where C_{Blood} is the mixed venous blood concentration of acrylamide or glycidamide (mM) and t_i is the exposure time (hours). Note, TWA as calculated above, is a time-integrated blood concentration, is conceptually equivalent to the area under the blood-time curve (AUC), and can be converted to units of AUC by multiplying the TWA by the time integration interval of interest. For example, if the TWA is multiplied by 24 hours, the resulting value is the AUC for 24 hours (mM 24 hours).

The general procedure for dosimetry extrapolation was as follows:

1. The rat model was used to simulate external rat dosages and to predict the corresponding internal dose metric, TWA concentrations of acrylamide and glycidamide in mixed venous blood.

2. In PBPK model simulations of the rat, acute-duration gavage doses (mg/kg/day) were assumed to be delivered as a single bolus administration each day at the exposure duration and frequency used in the acute-duration study (e.g., 5 consecutive days for the Sublet et al. 1989 study). Intermediate- and chronic-duration doses were assumed to be delivered during a daily 12-hour period (e.g., the daily food and water consumption period) for the entire exposure duration and frequency of the study (e.g., daily for 90 days for the Burek et al. [1980] study). Rat body weights were the TWA for the study.

3. The rat PBPK model simulations resulted in selection of a point of departure (POD) for dosimetry extrapolation (e.g., BMDL or NOAEL for TWA concentrations of acrylamide and glycidamide in mixed venous blood).

4. The human PBPK model was used to simulate the daily dosage (mg/kg/day) of acrylamide that corresponded to the POD. The human model was iterated for a series of ingestion doses until the selected value for the POD was predicted; the corresponding ingestion intake was the HED. A body weight of 70 kg was assumed for humans. Daily doses (mg/kg/day) in humans were assumed to be delivered in 12 consecutive hourly doses, separated by 12-hour intervals for the duration of the rat study. The intermediate-duration MRL is intended to be protective of human exposures up to 365 days, and the chronic-duration MRL is intended to be protective for human exposures exceeding 365 days; therefore, the HEDs for both intermediate- and chronic-duration MRLs were simulated as 365-day exposures. The elimination kinetics of acrylamide and glycidamide are relatively fast, resulting in a steady state within 1–2 days of repeated exposure; therefore, as the duration of the simulated exposure extends beyond several days, the TWA of acrylamide or glycidamide in blood approaches a constant value (see Figures A-1 and A-2).

Figure A-1. Simulation of Blood Acrylamide (AA) and Glycidamide (GA) Concentrations in a Rat Exposed to 1 mg Acrylamide/kg/day (Simulations Were for 12 Consecutive Hours of Exposure per Day)

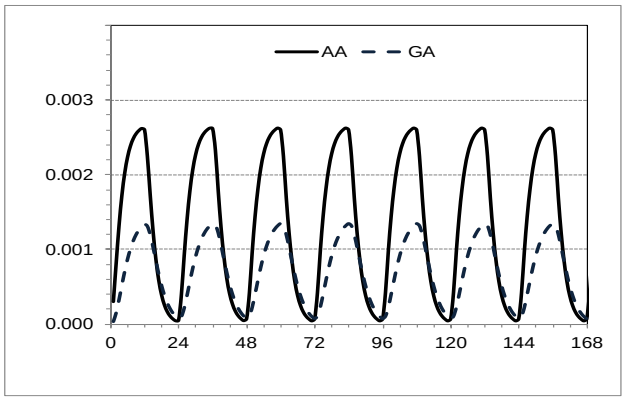
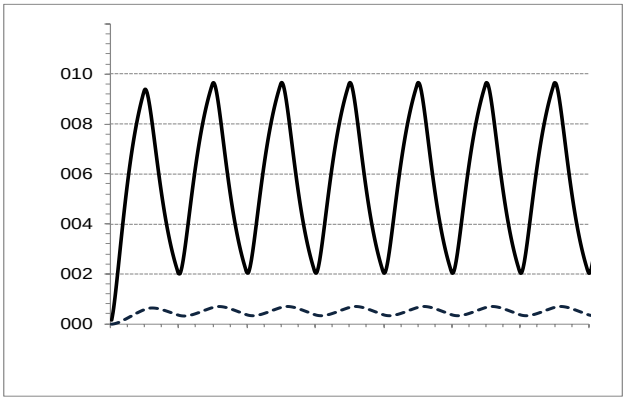


Figure A-2. Simulation of Blood Acrylamide (AA) and Glycidamide (GA) Concentrations in an Adult Human Exposed to 1 mg Acrylamide/kg/day (Simulations were for 12 Consecutive Hours of Exposure per Day)



The rationale for assuming a 12-hour dosing period in PBPK model simulations was the expectation that ingestion would occur only during a 12-hour (food and water) consumption period of the day. Other ingestion profiles could apply to specific individuals and populations. However, at the dose range of interest (<1 mg/kg/day), the model is essentially linear, which means that blood AUC has a very low dependence on dosing interval at a constant daily dose. For example, for an external dose of 1 mg/kg/day, decreasing the dosing interval from 12 hours (daily dose administered over a 12-hour period) to 24 hours results in a change in the TWA for acrylamide or glycidamide of <1%.

The PBPK models predict HEDs that are higher than equivalent rat doses when TWA for blood acrylamide is the internal dose metric and HEDs that are lower than equivalent rat doses when TWA for blood glycidamide is the internal dose metric (Figures A-3 and A-4). The HED:rat dose ratio is not a constant function of dose. At a dose of 1 mg/kg/day, the ratio is approximately 0.23 based on TWA for acrylamide in blood and 1.3 based on TWA for glycidamide in blood.

Figure A-3. Relationship Between Oral Dose of Acrylamide and Time-Weighted Average for Acrylamide in Blood in a Rat and Human (Simulations were for 12 Consecutive Hours of Exposure per Day for 365 Days)

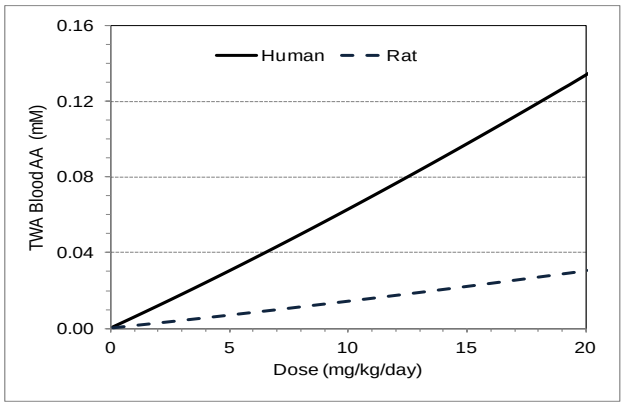
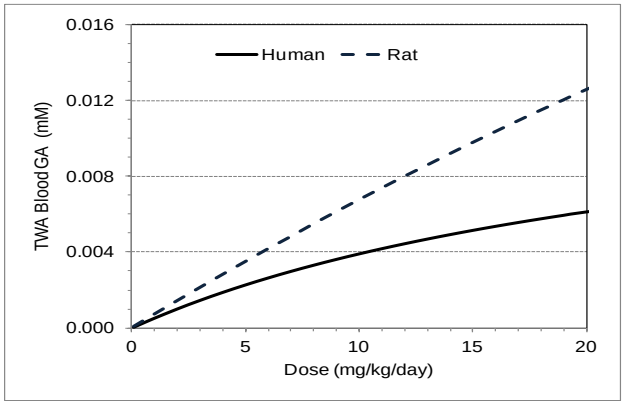


Figure A-4. Relationship Between Oral Dose of Acrylamide and Time-Weighted Average for Glycidamide in Blood in a Rat and Human (Simulations were for 12 Consecutive Hours of Exposure per Day for 365 Days)



APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Acrylamide
CAS Numbers: 79-06-1
Date: May 2012
Profile Status: Post-Public Comment Draft 3
Route: [ ] Inhalation [x] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 42
Species: Rat

Minimal Risk Level: 0.01 [x] mg/kg/day [ ] ppm

Reference: Sublet VH, Zenick H, Smith MK. 1989. Factors associated with reduced fertility and implantation rates in females mated to acrylamide-treated rats. Toxicology 55:53-67.

Experimental design: Groups of male Long-Evans hooded rats (15/group) were administered acrylamide (in distilled water) by oral gavage for 5 days at doses of 0, 30, 45, or 60 mg/kg/day (experiment 1) and 0, 5, or 15 mg/kg/day (experiment 2). Males were then mated on weeks 1, 2, 3, 4, 7, and 10 to proestrus females (weeks 1–4 only for experiment 2). Mating was confirmed by vaginal lavage. Females were sacrificed on gestation day 15 and numbers of corpora lutea, implantation sites, and fetuses were determined and estimates of pre- and postimplantation losses were calculated.

Effect noted in study and corresponding doses: Effects of acrylamide exposure on mating, fertility, and pre-and postimplantation losses are summarized in Table A-1. There were no significant treatment-related effects on mating index (number of sperm positive/number mated) at any dose level and no significant effects on any measures of reproductive success at the 5 mg/kg/day dose level. Assessments of reproductive indices at week 1 revealed significantly depressed fertility rates and elevated preimplantation losses at doses ≥15 mg/kg/day. Increased postimplantation loss was seen at weeks 2 and 3 at doses ≥15 mg/kg/day. In sperm samples collected from the 45 mg/kg/day group, the percentage of motile sperm was modestly (but significantly) decreased (58 vs. 73% in controls) at week 3, but not at weeks 2 or 4. This study identified a NOAEL of 5 mg/kg/day and a LOAEL of 15 mg/kg/day for significantly decreased fertility and increased preimplantation loss during week 1 posttreatment and significantly increased postimplantation loss during weeks 2 and 3 posttreatment.

Table A-1. Effects of Acrylamide on Selected Reproductive Indices Following Gavage Dosing of Male Long-Evans Rats for 5 Days

Treatment (mg/kg)	Post-treatment mating week	Mating index (percent)[a]	Fertility index (percent)[b]	Preimplantation loss index (percent)[c]	Postimplantation loss index (percent)[d]
Control[e]	1	25/30 (83)	22/25 (88)	19.57	4.20
	2	26/30 (87)	25/26 (96)	11.54	5.70
	3	29/30 (97)	28/29 (97)	11.46	6.80
	4	27/30 (90)	26/27 (96)	9.48	5.00
5	1	15/15 (100)	12/15 (80)	24.29	8.30
	2	14/15 (93)	11/14 (79)	25.40	10.80
	3	15/15 (100)	14/15 (93)	10.77	5.40
	4	13/15 (87)	11/13 (85)	17.08	7.10
15	1	13/15 (87)	6/13 (46)[f]	74.69[f]	10.30
	2	11/15 (73)	11/11 (100)	8.5	15.40[f]
	3	13/15 (87)	12/13 (92)	13.42	15.70[f]
	4	13/15 (87)	12/13 (92)	10.36	5.50
30	1	12/15 (80)	2/12 (17)[f]	97.83[f]	0.00
	2	15/15 (100)	15/15 (100)	15.90	25.40[f]
	3	15/15 (100)	14/15 (93)	14.51	35.00[f]
	4	15/15 (100)	15/15 (100)	4.90	17.50
45	1	13/15 (87)	2/13 (15)[f]	85.89[f]	26.77
	2	15/15 (100)	12/15 (80)	33.04[f]	60.77[f]
	3	15/15 (100)	10/15 (67)[f]	59.13[f]	55.50[f]
	4	15/15 (100)	15/15 (100)	11.60	7.67
60	1	15/15 (100)	1/15 (7)[f]	98.33[f]	33.33
	2	15/15 (100)	8/15 (53)[f]	73.39[f]	77.87[f]
	3	15/15 (100)	1/15 (7)[f]	98.80[f]	50.00[f]
	4	15/15 (100)	9/15 (60)[f]	70.84[f]	17.11[f]

[a]Mating index = number sperm/positive females/number mated.
[b]Fertility index = number pregnant/number sperm-positive females.
[c]Preimplantation loss = (number of corpora lutea/female – number of implant sites/female)/(number of corpora lutea/female) x100.
[d]Postimplantation loss = (number of implant sites/female – number of fetuses/females)/(number of implant sites/female) x100.
[e]Control data from "high" and "low" dose dominant lethal studies are combined for tabular presentation. However statistical differences associated with acrylamide treatment are based upon comparison with appropriate control group.
[f]$p \leq 0.05$.

Source: Sublet et al. 1989

Dose and end point used for MRL derivation: The MRL is based on a $BMDL_{10}$ of 0.00177669 mM (PBPK model-predicted rat blood TWA acrylamide dose) for decreased fertility in rats (as assessed by number of nonpregnant rats/number of sperm-positive females) following oral administration of acrylamide to male Long-Evans hooded rats for 5 days and subsequent mating with untreated female rats.

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

PBPK modeling was used to estimate rat internal dose metrics for blood acrylamide and glycidamide (a readily-formed metabolite of acrylamide in aqueous environment) for each of the administered acrylamide dose levels in the principal study and for estimating HEDs. Code for acrylamide and glycidamide rat and human PBPK models was provided by L.M. Sweeney along with data used to evaluate model performance and documentation of parameter values (Sweeney et al. 2010). Refer to Section 3.4.5 for a detailed description of the PBPK model of Sweeney et al. (2010).

For the 5-day gavage study of Sublet et al. (1989), the model was used for interspecies extrapolation of rat internal dosimetry to humans using the following procedure:

1. The rat model was used to simulate external rat dosages and to predict the corresponding internal dose metric, TWA concentrations of acrylamide and glycidamide in mixed venous blood, where TWA is calculated as follows:

$$TWA = \left(\int_{t=0}^{t=i} C_{Blood} \right) \div t_i$$

   where C_{Blood} is the mixed venous blood concentration of acrylamide or glycidamide (mM) and t_i is the exposure time (hours).

2. The gavage doses (mg/kg/day) were assumed to be delivered as a single bolus each day, at the exposure frequency (5 consecutive days) used in the study.

3. Rat internal doses (blood TWA) were estimated for the 5-day exposure duration (120 hours).

4. Rat body weight used in the simulations was 0.362 kg, which was the EPA (1988) reported mean body weight for 112-day-old male Long-Evans rats in a table (Table 3-4, page 3-72) used by EPA (1988) to generate a growth curve for male Long-Evans rats (Figure 3-26, page 3-88). The reported age of the male Long-Evans rats used in the 5-day gavage study of Sublet et al. (1989) was 90–100 days; additional body weight data were not included in the study report.

5. BMD modeling was performed to estimate the internal dose of the 95% lower confidence limit (BMDL) on the BMD for TWA acrylamide or glycidamide blood concentration in the rat.

6. The human model was used to predict the daily dosage (mg/kg/day) corresponding to the BMDL.

7. A body weight of 70 kg was assumed for humans.

8. Daily doses (mg/kg/day) in humans were assumed to be delivered in 12 consecutive hourly doses, separated by 12-hour intervals, on 5 consecutive days (the duration of the rat study).

9. Human external doses corresponding to the BMDLs were estimated for the 5-day exposure duration.

The PBPK model-predicted rat blood TWA acrylamide and glycidamide doses for each of administered dose levels used in the principal study (Sublet et al. 1989) are presented in Table A-2 along with the corresponding fraction of nonpregnant female rats (number of nonpregnant/number of sperm-positive females) at week 1 posttreatment, the time period shown to be most sensitive to male reproductive effects as demonstrated in Table A-1.

Table A-2. PBPK Model-Predicted Rat TWA Acrylamide and Glycidamide Doses to the Blood and Fraction of Nonpregnant Female Rats after 1 Week of Mating to Male Rats that had been Administered Acrylamide by Gavage for 5 Days Prior to Mating (Sublet et al. 1989)

Administered dose (mg/kg/day)	Rat blood TWA acrylamide dose (mM)	Rat blood TWA glycidamide dose (mM)	Fertility index[a]	Fraction of nonpregnant females[b]
0	0	0	22/25	3/25
5	0.00707	0.00335	12/15	3/15
15	0.0240	0.00881	6/13	7/13
30	0.0552	0.0148	2/12	10/12
45	0.0919	0.0193	2/13	11/13
60	0.133	0.0229	1/15	14/15

[a]Fertility index = number pregnant/number sperm-positive females.
[b]Number nonpregnant/number of sperm-positive females.

PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

The acute-duration oral MRL for acrylamide was derived using a BMD modeling approach. All dichotomous models in the EPA Benchmark Dose Software (Version 2.1.2) were fit to the incidence data for number of nonpregnant females/number of sperm-positive females using PBPK model-predicted rat TWA acrylamide dose to the blood as the dose metric; the models were also fit to the incidence data using PBPK model-predicted rat TWA glycidamide dose to the blood as the dose metric. A BMR of 10% extra risk was selected because the group sizes in this study (15 male rats/dose) did not support the application of a more sensitive BMR. Model results for the fraction of nonpregnant females are shown in Table A-3 for the rat blood acrylamide dose metric and Table A-4 for the rat blood glycidamide dose metric.

Table A-3. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Acrylamide and Fraction of Nonpregnant Female Rats after 1 Week of Mating to Male Rats that had been Administered Acrylamide by Gavage for 5 Days Prior to Mating (Sublet et al. 1989)

Model	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	Rat blood TWA acrylamide dose (mM)[c] BMD_{10}	$BMDL_{10}$
Gamma[d,e], Multistage[e,f], Weibull[d,e]	0.88	0.05	-0.41	0.72	85.86	0.0047264	0.00340605
Logistic	0.25	-0.40	1.15	1.16	89.81	0.011528	0.00850744
LogLogistic[g,h]	***0.94***	***0.07***	***-0.19***	***-0.46***	***87.04***	***0.00621986***	***0.00177669***
LogProbit[g]	0.96	0.03	0.23	-0.59	85.26	0.00782648	0.00536075
Probit	0.18	-0.44	1.21	1.40	90.69	0.0119204	0.00920888
						BMD_{05}	$BMDL_{05}$
LogLogistic[g,h]	***0.94***	***0.07***	***-0.19***	***-0.46***	***87.04***	***0.00381519***	***0.000841591***

[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]Rat blood acrylamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Sublet et al. (1989).
[d]Power restricted to ≥1.
[e]Gamma, multistage, and Weibull models took the form of a 1-degree multistage model and provided identical fit to the data.
[f]Betas restricted to ≥0.
[g]Slope restricted to ≥1.
[h]Selected model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were not sufficiently close (differed by >2–3-fold), so the model with the lowest BMDL was selected (LogLogistic).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-4. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Glycidamide and Fraction of Nonpregnant Female Rats after 1 Week of Mating to Male Rats that had been Administered Acrylamide by Gavage for 5 Days Prior to Mating (Sublet et al. 1989)

	X^2	Scaled residuals[b]				Rat blood TWA glycidamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.94	0.06	-0.17	0.44	87.04	0.0030958	0.000975396
Logistic[e]	***0.92***	***-0.14***	***-0.28***	***-0.56***	***85.53***	***0.00296497***	***0.00220167***
LogLogistic[f]	0.96	0.05	-0.10	-0.41	86.92	0.00363193	0.00143998
LogProbit[f]	0.96	0.05	-0.14	-0.39	86.94	0.00359742	0.00168997
Multistage (1-degree)[g]	0.71	0.37	-1.12	-1.12	86.96	0.00114806	0.000853692
Multistage (≥2-degree)[g]	0.86	0.12	-0.41	0.58	87.38	0.00235936	0.000945326
Probit	0.89	-0.14	-0.32	0.68	85.75	0.00283547	0.00218776
Weibull[d]	0.91	0.10	-0.30	0.51	87.18	0.00271645	0.000962598
						BMD_{05}	$BMDL_{05}$
Logistic[e]	***0.92***	***-0.14***	***-0.28***	***-0.56***	***85.53***	***0.00151342***	***0.000860953***

[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]Rat blood glycidamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Sublet et al. (1989).
[d]Power restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by >2–3-fold), so the model with the lowest AIC was selected (Logistic).
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Adequate model fit was judged by three criteria: X^2 goodness-of-fit p-value (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. As judged by X^2 goodness-of-fit statistic, all of the models provided adequate fit to the data. Comparing across models, the best fit to the data is generally indicated by the model with the lowest Akaike's Information Criteria (AIC) when BMDLs for all models providing adequate fit to the data differ from one another by <2–3-fold; otherwise, the model with the lowest BMDL is selected as the best-fitting model if it is not considered to be an outlier. For the modeled data using rat blood TWA acrylamide as the dose metric, the best-fitting model (log-logistic; lowest $BMDL_{10}$) provided a BMD_{10} of 0.00621986 mM and a $BMDL_{10}$ of 0.00177669 mM (Table A-3). BMD and BMDL values for a BMR of 5% extra risk from the best-fitting model are included in Table A-3 for comparison. For the modeled data using rat blood TWA glycidamide as the dose metric, the best-fitting model (logistic; lowest AIC) provided a BMD_{10} of 0.00296497 mM and a $BMDL_{10}$ of 0.00220167 mM (Table A-4). BMD and BMDL values for a BMR of 5% extra risk from the best-fitting model are included in Table A-4 for comparison.

Figure A-5 shows the plotted results for fraction of nonpregnant females during week 1 posttreatment from the best-fitting model (log-logistic) based on PBPK model-predicted rat blood TWA acrylamide

dose metric and a BMR of 10% extra risk. Figure A-6 shows the plotted results for fraction of nonpregnant females during week 1 posttreatment from the best-fitting model (logistic) based on PBPK model-predicted rat blood TWA glycidamide dose metric and a BMR of 10% extra risk.

Figure A-5. Fit of Log-Logistic Model to Fertility Data (Fraction of Nonpregnant Female Rats) at Week 1 Following 5 Days of Gavage Administration of Acrylamide to Male Rats Using Time-Weighted Average Acrylamide Blood Concentration (mM) as the Dose Metric and a Benchmark Response of 10% Extra Risk

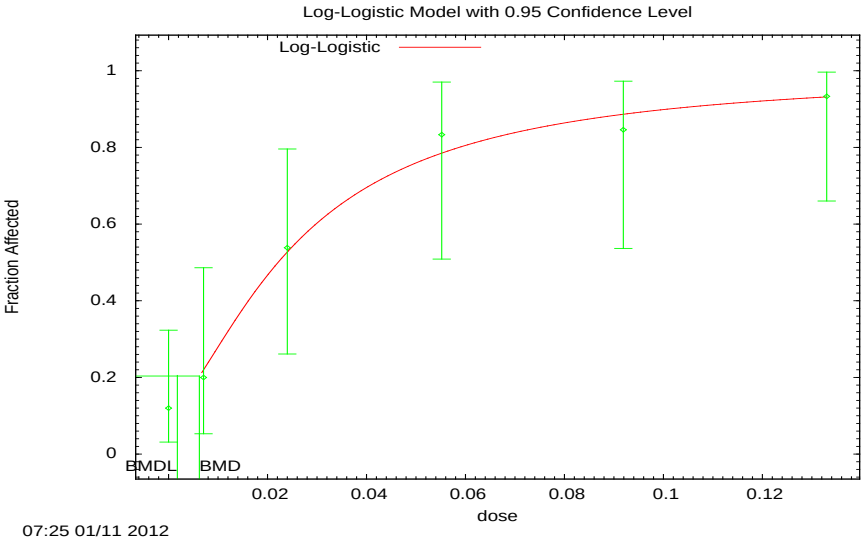
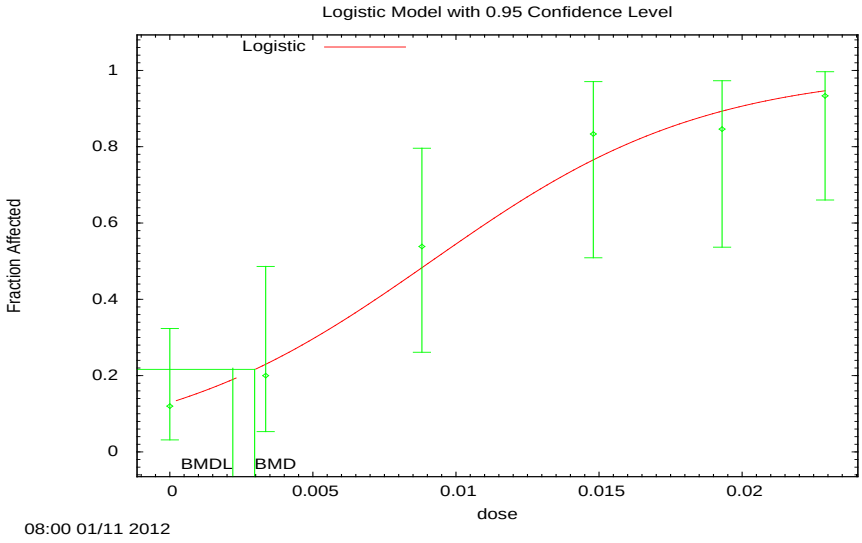


Figure A-6. Fit of Logistic Model to Fertility Data (Fraction of Nonpregnant Female Rats) at Week 1 Following 5 Days of Gavage Administration of Acrylamide to Male Rats Using Time-Weighted Average Glycidamide Blood Concentration (mM) as the Dose Metric and a Benchmark Response of 10% Extra Risk



Based on the rat blood TWA acrylamide $BMDL_{10}$ of 0.00177669 mM, the PBPK model-predicted HED is 0.31 mg acrylamide/kg/day and the rat equivalent dose is 1.33 mg acrylamide/kg/day. Based on the rat blood TWA glycidamide $BMDL_{10}$ of 0.00220167 mM, the PBPK model-predicted HED is 5.25 mg acrylamide/kg/day and the rat equivalent dose is 3.20 mg acrylamide/kg/day. Both acrylamide and glycidamide are widely distributed by the blood and both are reactive. However, based on uncertainty regarding the proximal toxicant(s) responsible for acrylamide-induced reproductive toxicity in the male rat, a conservative public health approach was taken and the lowest HED of 0.31 mg acrylamide/kg/day was selected as the POD for deriving an acute-duration oral MRL for acrylamide. A total uncertainty factor of 30 (3 for interspecies extrapolation using a PBPK model and 10 for human variability) was applied to the HED of 0.31 mg/kg/day, resulting in an acute-duration oral MRL of 0.01 mg/kg/day for acrylamide. An uncertainty factor of 10 for human variability is justified based on findings that key metabolic enzymes for acrylamide are CYP2E1, GST, and EH for which human polymorphisms are known (Huang et al. 2011a) and wide variation in human CYP2E1 expression as reviewed by Bolt et al. (2003).

Uncertainty Factors used in MRL derivation:

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

Was a conversion 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? No.

Other additional studies or pertinent information that lend support to this MRL: As demonstrated in Table 3-4 (Levels of Significant Exposure to Acrylamide – Oral), male-mediated implantation loss and decreased mean body weight gain represent the most sensitive effects of acute-duration oral exposure to acrylamide. The lowest dose level reported to induce significantly decreased male-mediated implantation loss was 15 mg/kg/day in male Long-Evans rats administered acrylamide by gavage for 5 days followed by mating sessions with unexposed female rats (Sublet et al. 1989); this study identified a NOAEL of 5 mg/kg/day. A similarly-designed study (Tyl et al. 2000b) confirmed the findings of acrylamide-induced increased implantation loss, although, based on pairwise comparisons with controls, statistical significance was achieved only at the highest dose level (60 mg/kg/day). Tyl et al. (2000b) also noted significantly decreased body weight gain (>40% lower than controls) during the 5 days of dosing, a finding not included in the study report of Sublet et al. (1989). Based on the reproducible results for male-mediated implantation loss in the studies of Sublet et al. (1989) and Tyl et al. (2000b) and the lack of supporting information regarding the body weight effects, the male-mediated decreased fertility was selected as the critical effect for deriving an acute-duration oral MRL for acrylamide. The study of Sublet et al. (1989) identified the lowest LOAEL for the critical effect and was therefore selected as the principal study.

Results of several other studies corroborate the findings of male-mediated decreases in fertility and increases in implantation losses following oral exposure to acrylamide (Chapin et al. 1995; Sakamoto and Hashimoto 1986; Smith et al. 1986; Tyl et al. 2000a; Zenick et al. 1986).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Acrylamide
CAS Numbers: 79-06-1
Date: May 2012
Profile Status: Post-Public Comment Draft 3
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 83
Species: Rat

Minimal Risk Level: 0.001 [x] mg/kg/day [ ] ppm

Reference: Burek JD, Albee RR, Beyer JE, et al. 1980. Subchronic toxicity of acrylamide administered to rats in the drinking water followed by up to 144 days of recovery. J Environ Pathol Toxicol 4(5-6):157-182.

Experimental design: Groups of 6-week-old male (23–29/group) and female (10/group) F344 rats were administered acrylamide in the drinking water for up to 93 days at concentrations designed to result in acrylamide intakes of 0, 0.05, 0.2, 1, 5, or 20 mg/kg/day. Ten rats/sex/group were assigned to the basic 90-day study and were observed for body weight and water consumption (recorded weekly) throughout the treatment period. Following 7 and 33 days of treatment, three control and three high-dose male rats were sacrificed for interim electron microscopic examination of the sciatic nerve. Ten male (nine in the high-dose group, due to one death prior to treatment termination) and all female rats from each treatment group were subjected to gross and histopathologic examination of all major organs and tissues at the end of the treatment period, at which time, three other male rats from each group were processed for electron microscopic examination of the sciatic nerve. The remaining rats (all males) in each group were observed for signs of recovery from treatment-related effects for up to 144 days following cessation of treatment. Three rats/group were subjected to electron microscopic examination of the sciatic nerve on recovery days 25, 111, and 144. Body weights were recorded for two rats/dose level prior to sacrifice on recovery day 111. At the end of the 144-day recovery period, the remaining four rats of each dose level were weighed and sacrificed for gross and histopathologic examination of all major organs and tissues.

All rats were observed daily (during the 5-day work week) for general health and clinical signs. Hindlimb foot splay was measured weekly in four control and four high-dose (20 mg/kg/day) male and female rats until the onset of neuropathy was detected, after which neuropathy in the high-dose group was monitored by clinical signs. After neuropathy was detected in high-dose rats, male and female rats in the 5 mg/kg/day dose groups were also subjected to weekly testing of foot splay (rats in the lower treatment groups were not tested due to the lack of response at 5 mg/kg/day). Blood samples collected from seven rats/sex in the control and high-dose groups on treatment day 76 and from all rats alive on day 60 of the recovery period were examined for packed cell volume, total erythrocyte count, total and differential leukocyte counts, and hemoglobin concentration. The study design included urinary sampling from 10 control and 10 high-dose rats per sex on treatment day 76 and at the end of the treatment period. Blood serum was collected from the 10 rats/sex/dose that were sacrificed at the end of treatment and from the 4 male rats/group that were maintained throughout the 144-day recovery period. Blood urea nitrogen, alkaline phosphatase, serum glutamic pyruvic transaminase, and serum cholinesterase activity were determined.

Light microscopic examinations were performed on brain, spinal cord, and peripheral nerves (including brachial plexus, sciatic, and femoral nerves) from selected male and female rats of each dose group. Nervous tissues were fixed in glutaraldehyde-paraformaldehyde and stained with hematoxylin eosin.

Additional sections of brain, spinal cord, and peripheral nerves were subjected to the luxol fast blue-periodic acid Schiff (LFB/PAS) reaction for myelin staining and to Bodian's stain to elucidate more subtle axonal changes. Myelin and axonal degeneration was classified as severe (degeneration in approximately 50% of the observed fibers), moderate (degeneration in 20–50% of observed fibers), slight (degeneration in <20% of observed fibers), very slight (effects restricted to focal or multifocal changes in individual nerves), or equivocal (nerves could not be graded as clearly normal). Only sciatic nerve tissues from male rats were examined by electron microscopy. Three blocks of sciatic nerve fibers, two longitudinal and one transverse, were selected per rat for thin sectioning and ultrastructural analysis. Ultrastructural alterations were counted by examining a maximum of 50 fields per block, a field defined as a section through any Schwann cell. This resulted in an examined maximum of 150 fields/rat or 450 fields/treatment group of three rats.

Hematology, urinary and clinical chemistry parameters, body weights, organ-to-body weight ratio data, foot spread results, and water consumption were statistically analyzed by one-way analysis of variance followed by Dunnett's test. The level of significance chosen was $p<0.05$. The study report did not, however, include individual or averaged incidences or extent of changes in these parameters, so an independent analysis of the results of body and organ weights, water consumption, foot splay, hematology, urinalysis, or serum chemistry was not possible.

Effect noted in study and corresponding doses: Significantly lower body weights were reported in the high-dose male and female rats relative to controls: 8% lower (males and females) on treatment days 13 and 20, and 21 and 24% lower (males and females, respectively) on treatment day 91. No significant body weight effect was seen in rats of lower dose groups. High-dose rats also exhibited treatment-related effects on organ weights including significantly decreased absolute liver, kidney, and thymus weights in males (also testicular) and females, significantly decreased absolute brain and heart weights in females (trend for decreased weights in males), increased relative brain, heart, liver, and kidney weights in males and females, and decreased relative thymus (females only) and testicular weight in males. Absolute and relative liver weight was increased in 5 mg/kg/day males. Marginally statistically significant increases in relative heart weight in 0.05 and 0.2 mg/kg/day females were not considered to be of toxicological significance due to the lack of a dose response. High-dose female rats exhibited significantly decreased water consumption (15–39% decreased) between treatment days 20 and 90. Although decreased water consumption was noted in high-dose males, the decrease reached the level of statistical significance in only 4 of the 13 intervals recorded. The few instances of significantly increased water consumption in low-dose rats did not follow a consistent pattern or trend, and may be of no toxicological significance. By day 144 of the posttreatment recovery period, the high-dose group had recovered with higher (but not statistically significant) body weights than controls, significantly higher absolute liver and kidney weights, and as significantly higher relative brain and liver weights.

Significantly increased instances of hindlimb foot splay were observed in high-dose male and female rats on treatment day 22 (incidences were not reported), which became more pronounced on treatment day 29. Foot splay testing was terminated with this treatment group (to prevent injury), but clinical signs of neuropathy (including curling of the toes, rear limb splay, incoordination, and posterior weakness) progressed in severity throughout the remainder of the treatment period. Beginning on treatment day 29, rats of the 5 mg/kg/day dose level were tested, but foot splay was not detected at this treatment level in either males or females. No other treatment-related clinical effects were observed in the 5 mg/kg/day males or females or any of the lower dose groups. By day 7 of the posttreatment recovery period, the high-dose groups showed clear signs of improvements continuing to day 111 with only slight posterior weakness and curling of the toes. By day 144, these high-dose rats appeared clinically similar to the controls.

At the end of the treatment period, serum cholinesterase activity was increased and alkaline phosphatase activity was statistically significantly increased in high-dose females. Significant decreases in packed cell volume, total erythrocyte count, and hemoglobin concentrations in high-dose males and females and 5 mg/kg/day females were noted. Results of urinalysis did not reveal any acrylamide-induced abnormalities. By day 144 posttreatment, the high-dose group (sex not specified) had statistically significant decreased serum cholinesterase levels and no significant differences in other clinical chemistry parameters.

Upon necropsy, gross observations of rats following the 92- or 93-day treatment period revealed treatment-related alterations only in the high-dose group, including perineal soiling, decreased adipose tissue, decreased liver size, darkened kidneys, foci or mottled appearance of lungs, decreased size or flaccid testicles, decreased size of male accessory genitalia, decreased uterus size, altered appearance of peripheral nerves, atrophy of skeletal muscle in the posterior portion of the body, bladder distention, and diffuse mural thickening of the stomach. The authors did not include incidence data regarding gross examination data, however. Histopathologic examination of high-dose rats revealed effects such as atrophy of skeletal muscle (2/10 males, 8/10 females), slightly increased hematogenous pigment in the spleen (4/9 males), ulcerative gastritis or hyperkeratosis in the nonglandular stomach (4/10 males), atrophy of mesenteric fat (8/10 females), vacuolization of the smooth muscle in the bladder wall (1/10 males, 2/9 females), inflammation in the lungs (3/10 males, 5/10 females), and testicular effects that included atrophy (10/10), mineralization in seminiferous tubules (5/10), and increased cellular debris and/or decreased spermatogenic segments in the tubular lamina of the epididymides (9/10). The statistical significance of these findings could not be assessed because incidence data for controls were not reported. By day 144 posttreatment, only the high-dose rats had persistent gross pathological effects, primarily dark testicles and slightly distended bladders. The testicular histological lesions consisted of focal or multifocal atrophy to individual seminiferous tubules, some with mineral and cellular debris, and indication of partial reversibility of the testicular atrophy. Light microscopic examination of the sciatic nerve sections (stained with hematoxylin and eosin) revealed severe degeneration in the high-dose groups that was characterized by demyelinization (LFB/PAS-treated sections) and axonal degeneration (Bodian's-treated sections) in 10/10 females and similar but less severe effects in males (degeneration moderate in 5/10 and severe in the other 5). These lesions were also seen in other peripheral nerve sections (brachial plexus and femoral nerve) but varied in severity from equivocal to severe (incidences not reported). The authors noted equivocal to very slight degenerative changes in peripheral nerves of 5 mg/kg/day males (9/10) and females (6/10) but found no light microscopic evidence of peripheral nerve lesions in 0.05, 0.2, or 1 mg/kg/day treatment groups. Very slight to slight degenerative changes (demyelinization, swollen astrocytes and axons) were seen in spinal cord sections of high-dose male (5/10) and female (9/10) rats. No treatment-related lesions were observed at any dose level within brain sections examined by light microscopy. After 144 days of posttreatment recovery, no nerve tissue alterations were observed in any of the 5 mg/kg/day or lower dose groups. In the high-dose group, alterations ranged from very slight to slight in the sciatic nerve and no alterations were noted in sections of the brachial nerve. The authors stated that if the recovery period had been extended beyond 144 days, the remaining tissue changes would likely have completely reversed.

Ultrastructural (electron microscope) examinations of sciatic nerve preparations from three male rats/group included the examination of fields (defined as a section through any Schwann cell) for signs of axolemma invaginations, axonal invaginations with cell organelles and/or dense bodies, and Schwann cells without axons and/or with degenerating myelin. After 7 days of treatment, no significant differences were seen between control and high-dose rats (other treatment groups were not subjected to 7-day interim sacrifice). After 33 days of treatment, high-dose male rats exhibited increased prevalence of fields showing axolemma invaginations with cell organelles and/or dense bodies and fields exhibiting Schwann cells without axons and/or with degenerating myelin (other groups were not subjected to 33-day interim sacrifice). Following 90 days of treatment, severe axonal degeneration and axonal loss were seen in high-

dose rats. Approximately 55% of the fields examined exhibited alterations in myelinated nerves or Schwann cells (compared with 12 and 21% after treatment days 7 and 33, respectively). Similar, but less severe, ultrastructural alterations in approximately 34% of the fields examined were seen in the 5 mg/kg/day dose group. At the 1 mg/kg/day dose level, approximately 24% of the fields examined showed axolemma invaginations with cell organelles and/or dense bodies, but not more severe signs of ultrastructural alterations. The alterations in the sciatic nerve fields examined in the control, 0.05, and 0.2 mg/kg-day groups were roughly comparable (15, 9, and 12%, respectively), suggesting that there were no adverse effects at the 0.05 and 0.2 mg/kg/day doses. Importantly, the increase in lesions observed via electron microscopy in the 1 and 5 mg/kg/day groups appeared to have completely reversed by days 25 and 111 posttreatment, respectively. The observed lesions in the high-dose group were partially or completely reversed by day 144 posttreatment.

In summary, the study of Burek et al. (1980) identified a NOAEL of 0.2 mg/kg/day and a LOAEL of 1 mg/kg/day, based on ultrastructural degeneration (axolemma invaginations with cell organelles and/or dense bodies) in the sciatic nerve of male rats (as detected by electron microscopic examinations, which were limited to males). The increased frequency was characterized by the study authors as "slight" for the LOAEL at 1 mg/kg/day, and the lesions were reversible (back to control levels) by day 25 posttreatment in all 1 mg/kg/day treated rats. At the resolution of the light microscope, the 5 mg/kg/day dose was the lowest dose resulting in degenerative effects in the sciatic nerve of male and female rats.

Dose and end point used for MRL derivation: 0.2 mg/kg/day

[x] NOAEL [ ] LOAEL

A NOAEL/LOAEL approach was selected because results of the ultrastructural evaluations included only 3 of 10 rats/group and were reported only as the total numbers of fields (per group) with ultrastructural changes as axolemma invaginations or Schwann cells without axons and/or with degenerating myelin. This reporting of the electron microscopy data does not support a statistical comparison of the incidence of changes between the exposed and control groups because the study report lacked information regarding the distribution of fields exhibiting alterations among the three rats within any particular dose group. Therefore, a BMD approach was not feasible.

PBPK modeling was used to estimate rat internal dose metrics for blood acrylamide and glycidamide at the acrylamide applied rat dose NOAEL of 0.2 mg/kg/day and for estimating HEDs. Code for acrylamide and glycidamide rat and human PBPK models was provided by L.M. Sweeney along with documentation of parameter values (Sweeney et al. 2010). The Sweeney et al. (2010) model is based on the acrylamide and glycidamide rat model reported by Kirman et al. (2003). Refer to Section 3.4.5 of the Toxicological Profile for Acrylamide for a detailed description of the PBPK model of Sweeney et al. (2010).

For the 90-day drinking water study of Burek et al. (1980), the model was used for interspecies extrapolation of rat internal dosimetry to humans using the following procedure:

1. The rat model was used to predict the internal dose metric, TWA concentration of acrylamide and glycidamide in mixed venous blood, corresponding to the administered acrylamide dose NOAEL of 0.2 mg/kg/day, where TWA is calculated as follows:

$$TWA = \left(\int_{t=0}^{t=i} C_{Blood} \right) \div t_i$$

where C_{Blood} is the mixed venous blood concentration of acrylamide or glycidamide (mM) and t_i is the exposure time (hours).

2. The oral dose (0.2 mg/kg/day) was assumed to be delivered during a daily 12-hour period (e.g., the daily food and water consumption period).

3. Rat internal doses (blood TWA) were estimated for the 90-day exposure duration (2,160 hours).

4. Rat body weight used in the simulation was the EPA (1988) subchronic reference body weight for the male F344 rat (0.180 kg) because quantitative body weight data were not included in the principal study report (Burek et al. 1980).

5. The human model was used to predict the daily human equivalent dose (HED in mg/kg/day) corresponding to the rat NOAEL of 0.2 mg/kg/day.

6. A body weight of 70 kg was assumed for humans.

7. The daily dose (mg/kg/day) in humans was assumed to be delivered in 12 consecutive hourly doses, separated by 12-hour intervals, 7 days/week for a duration of 365 days (upper end of the range for intermediate-duration MRL).

8. Human external doses corresponding to the PBPK model-predicted rat blood TWA acrylamide and TWA glycidamide doses at the rat NOAEL of 0.2 mg/kg/day were estimated for the 365-day exposure duration.

Based on PBPK model-predicted rat blood TWA acrylamide dose metric at the NOAEL of 0.2 mg acrylamide/kg/day, the HED is 0.038 mg acrylamide/kg/day. Based on the PBPK model-predicted rat blood TWA glycidamide dose metric at the NOAEL of 0.2 mg acrylamide/kg/day, the HED is 0.28 mg acrylamide/kg/day. Using a conservative approach, derivation of an intermediate-duration oral MRL for acrylamide was performed using the lowest HED of 0.038 mg acrylamide/kg/day. A total uncertainty factor of 30 (3 for interspecies extrapolation using a PBPK model and 10 for human variability) was applied to the HED of 0.038 mg/kg/day, resulting in an intermediate-duration oral MRL of 0.001 mg/kg/day.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans using dosimetric adjustment
[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? No.

Other additional studies or pertinent information that lend support to this MRL: Results of available animal studies demonstrate that neurological effects in males and females and reproductive effects in males are the most sensitive noncancer effects associated with intermediate-duration oral exposure to acrylamide (Burek et al. 1980; Chapin et al. 1995; Johnson et al. 1984, 1985, 1986; NTP 2011b;

Sakamoto and Hashimoto 1986; Smith et al. 1986; Tyl et al. 2000a, 2000b; Zenick et al. 1986). The lowest dose level reported to induce male-mediated implantation losses was 2.8 mg/kg/day in male Long-Evans rats receiving acrylamide from the drinking water for 80 days; this study identified a NOAEL of 1 mg/kg/day (Smith et al. 1986). Ultrastructural degenerative peripheral nerve changes were observed at a dose level as low as 1 mg/kg/day in male F344 rats receiving acrylamide from the drinking water for up to 93 days; this study identified a NOAEL of 0.2 mg/kg/day (Burek et al. 1980). Available data suggest that neurological effects represent a more sensitive point of departure than reproductive effects for deriving intermediate- and chronic-duration oral MRLs for acrylamide. Therefore, degenerative nerve change was selected as the critical effect for deriving an intermediate-duration oral MRL for acrylamide. The study of Burek et al. (1980) was selected as the principal study because it identified the lowest LOAEL for the critical effect. A NOAEL/LOAEL approach was selected because results of the ultrastructural evaluations included only 3 of 10 rats/group and were reported only as the total numbers of fields (per group) with ultrastructural changes as axolemma invaginations or Schwann cells without axons and/or with degenerating myelin. This reporting of the electron microscopy data does not support a statistical comparison of the incidence of changes between the exposed and control groups because it is unknown within any exposure group how the numbers of changes were distributed among the three rats (i.e., whether the apparent increase in incidence of fields with changes was due to one, two, or all three rats in the 1, 5, and 20 mg/kg-day groups). Therefore, a BMD approach was not feasible.

Interim data from a chronic toxicity and carcinogenicity bioassay of male and female F344 rats receiving acrylamide from the drinking water for up to 2 years (Johnson et al. (1984, 1985, 1986) provide support to the findings of Burek et al. (1980). In the 2-year study, interim sacrifices were performed at 3, 6, 12, and 18 months on some rats from each exposure group. One aspect of interim sacrifices was to evaluate the condition of selected peripheral nerve sections using light and electron microscopy. The most significant noncancer effects were increased incidences of axolemma invaginations (observed by electron microscopy) in the tibial branch of the sciatic nerve of male rats following 3 and 6 months of treatment and increased prevalence of "moderate" to "severe" degeneration (observed by light microscopy) in both males and females following 2 years of treatment. This study identified a NOAEL of 0.5 mg/kg/day and a LOAEL of 2.0 mg/kg/day for light and electron microscope evidence of peripheral nerve fiber degeneration in the male rats. Electron microscope evaluations at interims ≥12 months were not considered meaningful due to age-related degenerative effects that could not be distinguished from acrylamide-induced effects.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Acrylamide
CAS Numbers: 79-06-1
Date: May 2012
Profile Status: Post-Public Comment Draft 3
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [ ] Intermediate [x] Chronic
Graph Key: 154
Species: Rat

Minimal Risk Level: 0.001 [x] mg/kg/day [ ] ppm

Reference: Friedman MA, Dulak LH, Stedham MA. 1995. A lifetime oncogenicity study in rats with acrylamide. Fundam Appl Toxicol 27(1):95-105.

Experimental design:

Groups of male and female F344 rats (≥50/sex/group) were exposed to acrylamide in the drinking water for 2 years at concentrations resulting in calculated doses of 0, 0.1, 0.5, or 2.0 mg/kg/day for the males and 0, 0.5, or 3.0 mg/kg/day for the females. The study included two control groups for each sex to assess variability in background tumor responses and 204 male rats in the 0.1 mg/kg/day group to increase the statistical power sufficient to detect a 5% increase in incidence of scrotal sac mesotheliomas over an expected background incidence of this tumor for F344 rats of about 1%. The study also had different dose group spacing for female rats to improve the characterization of the dose-response relationships. An additional group of 25 rats/sex was observed during the course of this study for signs of viral infections. Water and food intakes and body weights were monitored throughout the study. All animals were observed twice daily for mortality, morbidity, and obvious clinical signs of toxicity; periodic physical examinations were performed. Complete postmortem gross pathologic examinations were performed on all rats in the study. Brain, liver, kidneys, and testes were excised and weighed. Group mean organ weights and organ-to-body weight ratios were calculated. Representative sections from all major organs and tissues (including the sciatic nerve) were processed for histopathologic examination. Initially, light microscopic examination was completed only on high-dose and control rats. Based on histopathologic results in these groups, examinations were performed on specific tissues harvested from rats of lower dose groups. Histopathologic examination was performed on thyroid, brain (three levels, females only), mammary glands (females), and testes (males) in all rats. In addition, spinal cord (three levels), uterus, and gross lesions were evaluated in all control and high-dose females, and in low-dose female rats found dead or sacrificed moribund. Brain (three levels), spinal cord (three levels), and gross lesions were examined in all control and high-dose males and in low- and mid-dose male rats found dead or sacrificed moribund. No special staining methods were used to enhance light microscopic detection of degenerative changes in nervous tissues.

Effect noted in study and corresponding doses: The most sensitive noncancer effect was degenerative changes in the sciatic nerve as detected by light microscopy. The study identified a NOAEL of 0.5 mg/kg/day and a LOAEL of 2.0 mg/kg/day for the males and a NOAEL of 1.0 mg/kg/day and a LOAEL of 3.0 mg/kg/day for the female rats. Incidence data for degenerative changes in the sciatic nerve of the male and female rats are presented in Table A-5.

Table A-5. Incidence Data for Degenerative Changes in Sciatic Nerve Preparations from F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years

Sciatic nerve degenerative changes	Dose (mg/kg/day)						
	0	0	0.1	0.5	1.0	2.0	3.0
Males	30/83	29/88	21/65	13/38		26/49[a]	
Females	7/37	12/43			2/20		38/86[b]

[a]Significantly ($p<0.05$) different from control incidence by Fisher's exact test performed by SRC, Inc.; incidences for the two control groups were pooled.
[b]Significantly ($p<0.01$) different from control incidence by Fisher's exact test performed by SRC, Inc.; incidences for the two control groups were pooled.

Source: Friedman et al. 1995

Dose and end point used for MRL derivation: The MRL is based on a $BMDL_{05}$ of 0.000240096 mM (PBPK model-predicted rat blood TWA acrylamide dose) for degenerative sciatic nerve changes in male F344 rats administered acrylamide in the drinking water for up to 2 years.

[ ] NOAEL [ ] LOAEL [x] $BMDL_{05}$

PBPK modeling was used to estimate rat internal dose metrics for blood acrylamide and glycidamide at the each of the administered acrylamide doses and for estimating HEDs. Code for acrylamide and glycidamide rat and human PBPK models was provided by L.M. Sweeney along with documentation of parameter values (Sweeney et al. 2010). Refer to Section 3.4.5 for a detailed description of the PBPK model of Sweeney et al. (2010).

For the 2-year drinking water study of Friedman et al. (1995), the model was used for interspecies extrapolation of rat internal dosimetry to humans using the following procedure:

1. The rat model was used to simulate external rat dosages and to predict the corresponding internal dose metric, TWA concentrations of acrylamide and glycidamide in mixed venous blood, where TWA is calculated as follows:

$$TWA = \left(\int_{t=0}^{t=i} C_{Blood} \right) \div t_i$$

where C_{Blood} is the mixed venous blood concentration of acrylamide or glycidamide (mM) and t_i is the exposure time (hours).

2. The rat oral doses were assumed to be delivered during a daily 12-hour period.

3. Rat internal doses (blood TWA) were estimated for the 2-year exposure duration (17,250 hours).

4. Rat body weights used in the simulation were the time-weighted average body weights for each dose group calculated from quantitative body weight data provided in Dulak et al. (1989).

5. The human model was used to predict the daily dosage (mg/kg/day) corresponding to the 95% lower confidence limit (BMDL) on the BMD for TWA acrylamide or glycidamide blood concentration in the rat.

6. A body weight of 70 kg was assumed for humans.

7. The daily dose (mg/kg/day) in humans was assumed to be delivered in 12 consecutive hourly doses, separated by 12-hour intervals, 7 days/week for a duration of 366 days (lower end of the chronic MRL duration for humans and sufficient duration to achieve unchanging values for the human dose with increasing exposure duration).

8. Human external doses corresponding to the BMDLs were estimated for the 366-day exposure duration.

Administered dose, predicted corresponding rat blood TWA acrylamide and glycidamide doses, and degenerative sciatic nerve incidence data from the study of Friedman et al. (1995) are shown in Table A-6.

Table A-6. PBPK Model-Predicted Rat TWA Blood Acrylamide and Glycidamide Doses and Incidences of Degenerative Sciatic Nerve Changes in Male and Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years

Ingested acrylamide dose (mg/kg/day)	Rat blood TWA acrylamide dose (mM)	Rat blood TWA glycidamide dose (mM)	Number of rats	Number of rats affected
Males				
0	0	0	171	59
0.1	0.000135	0.0000732	65	21
0.5	0.000675	0.000365	38	13
2.0	0.00268	0.00142	49	26
Females				
0	0	0	80	19
1.0	0.00119	0.000652	20	2
3.0	0.00358	0.00191	86	38

PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Source: Friedman et al. 1995

The chronic-duration oral MRL for acrylamide was derived using a BMD modeling approach. All dichotomous models in the EPA Benchmark Dose Software (Version 2.1.2) were fit to the incidence data for degenerative sciatic nerve changes in the male and female F344 rats of the principal study (Friedman et al. 1995) using predicted rat blood TWA acrylamide as the dose metric and also using rat blood TWA glycidamide as the dose metric. A BMR of 10% extra risk was selected for initial BMD modeling. Adequate model fit was judged by three criteria: X^2 goodness-of-fit p-value ($p>0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Comparing across models within a particular dataset, the best fit to the data is generally indicated by the model with the lowest AIC when BMDLs for all models providing adequate fit to the data differ

from one another by <2–3-fold; otherwise, the model with the lowest BMDL is selected as the best-fitting model if it is not considered to be an outlier. The best-fitting model for each dataset was then fit to the incidence data for degenerative sciatic nerve changes using a BMR of 5% extra risk because sufficient numbers of rats were used (≥38/dose group with the exception of 20 for the 1.0 mg/kg/day group of female rats). The BMD modeling results for the male and female rats using blood TWA acrylamide as the dose metric are presented in Tables A-7 and A-8, respectively. The BMD modeling results for the male and female rats using blood TWA glycidamide as the dose metric are presented in Tables A-9 and A-10, respectively.

Table A-7. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Acrylamide and Incidence of Degenerative Changes in Sciatic Nerve Preparations from Male F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of Friedman et al. (1995)

	χ^2	Scaled residuals[b]				Rat blood TWA acrylamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.75	0.002	0.00	-0.271	424.82	0.00174413	0.000493189
Logistic	0.80	-0.45	0.12	-0.45	423.16	0.000982251	0.000613461
LogLogistic[e]	0.75	0.004	0.00	-0.272	424.82	0.00180899	0.000411211
LogProbit[e]	0.75	0.00	0.00	-0.271	424.82	0.00163947	0.000816335
Multistage (1-degree)[f]	0.75	-0.54	0.18	-0.54	423.29	0.000868289	0.000471031
Multistage (2-degree)[f]	0.94	-0.12	0.01	-0.26	422.84	0.00148538	0.000492016
Multistage (3-degree)[f,g]	***0.95***	***-0.005***	***0.00***	***-0.27***	***422.82***	***0.00180927***	***0.000493176***
Probit	0.80	-0.46	0.12	-0.46	423.16	0.000974583	0.000607024
Weibull[d]	0.75	0.004	0.00	-0.27	424.82	0.00185484	0.000493183
						BMD_{05}	$BMDL_{05}$
Multistage (3-degree)[f,g]	***0.95***	***-0.005***	***0.00***	***-0.27***	***422.82***	***0.0014233***	***0.000240096***

[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]Rat blood TWA acrylamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Friedman et al. (1995).
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models provided adequate fit to the data as judged by X^2 goodness-of-fit p-value (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. BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Multistage 3-degree).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-8. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Glycidamide and Incidence of Degenerative Changes in Sciatic Nerve Preparations from Male F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of Friedman et al. (1995)

	χ^2	Scaled residuals[b]				Rat blood TWA glycidamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.75	0.002	0.00	-0.27	424.82	0.000929055	0.000262417
Logistic	0.80	-0.46	0.12	-0.46	423.17	0.000521154	0.000325441
LogLogistic[e]	0.75	0.003	0.00	-0.27	424.82	0.000963337	0.000219382
LogProbit[e]	0.75	0.00	0.00	-0.27	424.82	0.000874854	0.000433150
Multistage (1-degree)[f]	0.75	-0.55	0.19	0.55	423.31	0.000461251	0.000250180
Multistage (2-degree)[f]	0.94	-0.13	0.01	-0.25	422.84	0.000787078	0.000261731
Multistage (3-degree)[f,g]	***0.95***	***-0.008***	***0.00***	***-0.27***	***422.82***	***0.000958606***	***0.000262409***
Probit	0.80	-0.47	0.12	-0.47	423.18	0.000517105	0.000322016
Weibull[d]	0.75	0.004	0.00	-0.27	424.82	0.000987529	0.000262414
						BMD_{05}	$BMDL_{05}$
Multistage (3-degree)[f,g]	***0.95***	***-0.008***	***0.00***	***-0.27***	***422.82***	***0.00075411***	***0.00012775***

[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]Rat blood TWA glycidamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Friedman et al. (1995).
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models provided adequate fit to the data as judged by X^2 goodness-of-fit p-value (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. BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Multistage 3-degree).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-9. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Acrylamide and Incidence of Degenerative Changes in Sciatic Nerve Preparations from Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of Friedman et al. (1995)

	χ^2	Scaled residuals[b]				Rat blood TWA acrylamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d,e]	***0.18***	***-1. 21***	***0.00***	***-1.21***	***224.85***	***0.00296422***	***0.00110863***
Logistic	0.06	-1.73	0.25	-0.73	226.85	0.00146242	0.00109037
LogLogistic[f]	NA	-1.21	0.00	-1.21	226.85	0.00324757	0.00111234
LogProbit[f]	NA	-1.21	0.00	-1.21	226.85	0.00301355	0.00139081
Multistage (1-degree)[g]	0.05	0.51	0.40	-1.87	227.45	0.00123757	0.00077607
Multistage (2-degree)[g]	0.11	-1.46	0.12	-1.46	225.68	0.00200634	0.00092149
Probit	0.06	-1.75	0.26	-1.75	226.92	0.00143256	0.00105280
Weibull[d]	NA	-1.21	0.00	-1.21	226.85	0.00327830	0.00110853
						BMD_{05}	$BMDL_{05}$
Gamma[d,e]	***0.18***	***-1.21***	***0.00***	***-1.21***	***224.85***	***0.00268972***	***0.000542603***

[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]Rat blood TWA acrylamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Friedman et al. (1995).
[d]Power restricted to ≥1.
[e]Selected model. The only models that provided adequate fit to the data were the Gamma and Multistage 2-degree (χ^2 goodness-of-fit p-value >0.1). BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Gamma).
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-10. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Glycidamide and Incidence of Degenerative Changes in Sciatic Nerve Preparations from Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of Friedman et al. (1995)

	χ^2	Scaled residuals[b]				Rat blood TWA glycidamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d,e]	***0.18***	***-1.21***	***0.00***	***-1.21***	***224.85***	***0.001581470***	***0.000608521***
Logistic	0.06	-1.74	0.26	-0.74	226.91	0.000781896	0.000582625
LogLogistic[f]	NA	-1.21	0.00	-1.21	226.85	0.001736800	0.000610443
LogProbit[f]	NA	-1.21	0.00	-1.21	226.85	0.001612570	0.000747637
Multistage (1-degree)[g]	0.05	0.51	0.41	-1.89	227.52	0.000663165	0.000415425
Multistage (2-degree)[g]	0.11	-1.47	0.13	-1.47	225.73	0.001071610	0.000495119
Probit	0.06	-1.76	0.27	-1.76	226.98	0.000765892	0.000562600
Weibull[d]	NA	-1.21	0.00	-1.21	226.85	0.001752310	0.000608403
						BMD_{05}	$BMDL_{05}$
Gamma[d,e]	***0.18***	***-1.21***	***0.00***	***-1.21***	***224.85***	***0.00143502***	***0.000302968***

[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]Rat blood glycidamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Friedman et al. (1995).
[d]Power restricted to ≥1.
[e]Selected model. The only models that provided adequate fit to the data were the Gamma and Multistage 2-degree (χ^2 goodness-of-fit p-value >0.1). BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Gamma).
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

The best-fitting model results for incidence of light microscope-detected degenerative sciatic nerve changes in the male and female F344 rats from the principal study (Friedman et al. 1995) using rat blood TWA acrylamide as the dose metric and rat blood TWA glycidamide as the dose metric are summarized in Table A-11. The human PBPK model (Sweeney et al. 2010) model was then used to predict the daily HED (in mg/kg/day) corresponding to the 95% lower confidence limit ($BMDL_{10}$ and $BMDL_{05}$) on the BMD_{10} and BMD_{05} for PBPK model-predicted rat blood TWA acrylamide dose and for PBPK model-predicted rat blood TWA glycidamide dose. The corresponding PBPK model-predicted rat external doses and HEDs are also presented in Table A-11.

Table A-11. Summary of BMDL Values and Corresponding Rat External Doses and HEDs from the Best-Fitting Models for Incidences of Degenerative Changes in Sciatic Nerves Using Rat PBPK Model-Predicted Blood TWA Acrylamide as the Dose Metric and Glycidamide as the Dose Metric for the Male and Female F344 Rats from the Principal Study (Friedman et al. (1995)

Parameter	Rat blood TWA acrylamide-based BMDL (mM)	Rat dose[a] (mg/kg/day)	HED (mg/kg/day)	Rat blood TWA glycidamide-based BMDL (mM)	Rat dose[a] (mg/kg/day)	HED (mg/kg/day)
Male rat $BMDL_{10}$	0.000493176	0.37	0.085	0.000262417	0.36	0.49
Female rat $BMDL_{10}$	0.00110863	0.93	0.19	0.000608521	0.93	1.17
Male rat $BMDL_{05}$	0.000240096	0.18	0.042	0.00012775	0.18	0.24
Female rat $BMDL_{05}$	0.000542603	0.46	0.094	0.000302968	0.46	0.57

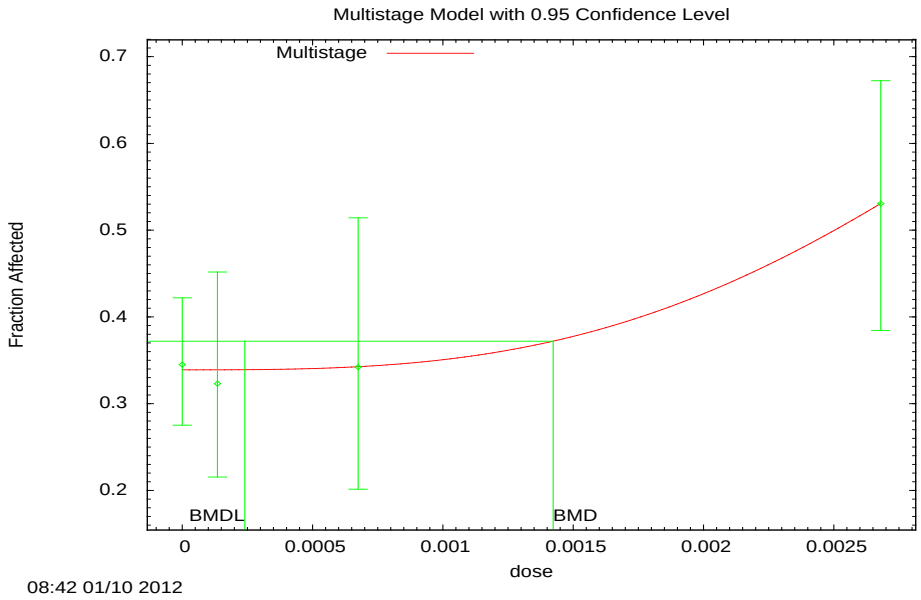
[a]Rat dose is the PBPK model-predicted dose of acrylamide corresponding to the PBPK model-predicted HED at the BMD-predicted rat blood TWA acrylamide- or glycidamide-based BMDL.

BMDL = 95% lower confidence limit on the benchmark dose (BMD), which is the maximum likelihood estimate of the exposure concentration associated with the selected benchmark response (subscripts denote benchmark response: e.g., $_{05}$ = exposure concentration associated with 5% extra risk); HED = human equivalent dose; TWA = time-weighted average

As stated previously, a BMR of 5% extra risk is justified because the principal study (Friedman et al. 1995) used sufficient numbers of animals. Comparing the PBPK model-predicted HEDs for the male and female rats of the principal study using blood TWA acrylamide as the dose metric and blood TWA glycidamide as the dose metric, the lowest HED is 0.042 mg/kg/day based on PBPK model-predicted blood TWA acrylamide ($BMDL_{05}$ of 0.000240096 mM) for the male rats. The HED of 0.042 mg/kg/day was selected as the POD for deriving a chronic-duration oral MRL for acrylamide because it represents the most public health protective POD. The HED of 0.042 mg/kg/day was divided by a total uncertainty factor of 30 (3 for interspecies extrapolation using a PBPK model and 10 for human variability), resulting in a chronic-duration oral MRL of 0.001 mg/kg/day for acrylamide. An uncertainty factor of 10 for human variability is justified based on findings that key metabolic enzymes for acrylamide are CYP2E1, GST, and microsomal EH for which human polymorphisms are known (Huang et al. 2011a) and wide variation in human CYP2E1 expression as reviewed by Bolt et al. (2003).

Figure A-7 shows the plotted results from the best-fitting model (Multistage 3-degree; Table A-7) for PBPK model-predicted blood TWA acrylamide and degenerative sciatic nerve changes in the male rats from the study of Friedman et al. (1995).

Figure A-7. Fit of Multistage (3-degree) Benchmark Dose Model to Data on the Incidence of Degenerative Peripheral Nerve Changes in Male F344 Rats Exposed to Acrylamide in the Drinking Water for up to 2 Years Using Time-Weighted Average Acrylamide Blood Concentration (mM) as the Dose Metric and a BMR of 5% Extra Risk



Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 3 for extrapolation from animals to humans using dosimetric adjustment
[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? No.

Other additional studies or pertinent information that lend support to this MRL: Two other chronic toxicity and carcinogenicity drinking water studies that employed male and female F344 rats (Johnson et al. 1986; NTP 2011b) reported acrylamide-induced degenerative peripheral nerve changes at doses in the same range as those eliciting degenerative sciatic nerve changes in the rats of the principal study (Friedman et al. 1995). The incidence data for degenerative peripheral nerve changes in the rats from these additional studies were subjected to the same PBPK modeling and BMD analysis as those employed using results from the principal study (Friedman et al. 1995). Relevant study details and results of PBPK modeling and BMD modeling of the data from the studies of Johnson et al. (1986) and NTP (2011b) follow.

In the chronic toxicity and carcinogenicity study of Johnson et al. (1986), groups of F344 rats (90/sex/treatment group) were exposed acrylamide in the drinking water at concentrations calculated to

provide doses of 0, 0.01, 0.1, 0.5, or 2.0 mg/kg-day for up to 2 years. Ten rats/sex/treatment group were randomly selected for interim sacrifices after 6, 12, or 18 months of treatment. The remaining rats (60/sex/treatment group) were subjected to comprehensive histopathological evaluations at death or terminal sacrifice. The evaluations included light and electron microscope examinations of three separate peripheral nerves (tibial nerve and two unspecified nerves), three locations of the spinal cord, and six sections through the brain and olfactory bulbs.

Light microscopic examination of peripheral nerve section revealed degenerative changes that consisted of focal swelling of individual nerve fibers with fragmentation of the myelin and axon and formation of vacuoles containing small round eosinophilic globules and macrophages. The study authors graded nerve degeneration as very slight, slight, moderate, or severe but did not further characterize the grading scheme. "Minimal" tibial nerve degeneration was observed in control and all treated groups beginning at the 12-month necropsy. Incidences of nerve degeneration increased in controls and treated groups alike throughout the remainder of the treatment period. Table A-12 summarizes the light microscopic findings in tibial nerve sections of the groups of rats from the main study that were treated for up to 2 years. Pairwise comparisons between acrylamide-treated groups and controls revealed no significant differences regarding incidences of histopathologic nerve lesions in any group of treated males or females at treatment levels <2.0 mg/kg/day. A statistically significant increase in pooled incidence of slight-to-moderate degeneration was noted in tibial nerves for 2.0 mg/kg/day females.

Table A-12. Incidence Data for Degenerative Changes in Tibial Nerve Preparations from F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years

Severity of degenerative change	Dose (mg/kg/day)				
	0	0.01	0.1	0.5	2.0
Males					
Very slight	30/60	29/60	23/60	25/60	19/60
Slight	19/60	22/60	21/60	19/60	21/60
Moderate	8/60	5/60	12/60	13/60	12/60
Severe	1/60	1/60	0/60	0/60	4/60
Moderate + severe[a]	9/60	6/60	12/60	13/60	16/60
Females					
Very slight	45/60	43/60	45/60	42/60	37/61
Slight	3/60	7/60	5/60	7/60	13/61
Moderate	0/60	0/60	0/60	0/60	3/61
Slight + moderate	3/60	7/60	5/60	7/60	16/61[b]

[a]Statistically significant trend for increased incidence with increasing dose by Mantel-Haenszel extension of the Cochran-Armitage test; p<0.01.
[b]Significantly different from control incidence by Fisher's exact test performed by SRC, Inc.; p<0.01.

Source: Johnson et al. 1986

Electron microscopic examinations of peripheral nerve sections from rats in the groups destined for independent neuropathologic assessment revealed slightly increased incidences of axolemma invaginations in 2.0 mg/kg-day male (but not female) rats, relative to controls, at 3- and 6-month interim sacrifices. There were no indications of treatment-related degenerative effects at lower treatment levels. At 12-month interim examination, degenerative myelin and axonal changes were observed in controls as well as all treatment groups and were considered to be the result of aging. High background incidences of

degenerative changes at 18 and 24 months precluded the usefulness of electron microscopic analysis to detect differences between control and exposed groups.

The chronic study of Johnson et al. (1986) identified a NOAEL of 0.5 mg/kg/day and a LOAEL of 2.0 mg/kg/day for significantly increased incidences of degenerative tibial nerve changes in the female rats. Although the male rats exhibited a significant trend for increasing incidences of degenerative tibial nerve changes with increasing dose, incidences in the acrylamide-treated males were not significantly different from the incidence in the control males.

The PBPK model-predicted rat blood TWA acrylamide and glycidamide doses and corresponding incidence data for degenerative tibial nerve changes in male and female F344 rats are shown in Table A-13. BMD modeling results from the study of Johnson et al. (1986) using blood TWA acrylamide as the dose metric and using blood TWA glycidamide as the dose metric are presented in Tables A-14 and A-15, respectively for the male rats, and Tables A-16 and A-17, respectively, for the female rats.

Table A-13. PBPK Model-Predicted Rat TWA Blood Acrylamide and Glycidamide Doses and Incidences of Degenerative Tibial Nerve Changes in Male and Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years

Ingested acrylamide dose (mg/kg/day)	Rat blood TWA acrylamide dose (mM)	Rat blood TWA glycidamide dose (mM)	Number of rats	Number of rats affected[a]
Males				
0	0	0	60	9
0.01	0.0000135	0.00000737	60	6
0.1	0.000135	0.0000735	60	12
0.5	0.000678	0.000366	60	13
2.0	0.00273	0.00144	60	16
Females				
0	0	0	60	3
0.01	0.0000135	0.00000652	60	7
0.1	0.000135	0.0000656	60	5
0.5	0.000678	0.000325	60	7
2.0	0.00273	0.00128	61	16

[a]Incidences in males are for the combined severity categories of moderate+severe; incidences in females are for the combined severity categories of slight+moderate.

PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Source: Johnson et al. 1986

Table A-14. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Acrylamide and Incidence of Degenerative Changes in Tibial Nerve Preparations from Male F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of Johnson et al. (1986)

	χ^2	Scaled residuals[b]				Rat blood TWA acrylamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.48	0.60	-0.25	-1.15	288.66	0.00175067	0.000880355
Logistic	0.44	0.70	-0.18	-1.21	288.89	0.00201959	0.00123132
LogLogistic[e,f]	***0.49***	***0.56***	***-0.27***	***-1.13***	***288.59***	***0.00166439***	***0.000774339***
LogProbit[e]	0.33	0.98	-0.09	-1.34	289.67	0.00235132	0.00144244
Multistage (1-degree)[g]	0.48	0.60	-0.25	-1.15	288.66	0.00175071	0.000880355
Multistage (2-degree)[g]	0.48	0.60	-0.25	-1.15	288.66	0.00175071	0.000880355
Multistage (3-degree)[g]	0.48	0.60	-0.25	-1.15	288.66	0.00175071	0.000880355
Multistage (4-degree)[g]	0.48	0.60	-0.25	-1.15	288.66	0.00175071	0.000880355
Probit	0.45	0.69	-0.19	-1.20	288.86	0.00198498	0.00118383
Weibull[d]	0.48	0.60	-0.25	-1.15	288.66	0.00175071	0.000880355
						BMD_{05}	$BMDL_{05}$
LogLogistic[e,f]	***0.49***	***0.56***	***-0.27***	***-1.13***	***288.59***	***0.000788397***	***0.000366792***

[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]Rat blood TWA acrylamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Johnson et al. (1986).
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. All models provided adequate fit to the data as judged by X^2 goodness-of-fit p-value (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. BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (LogLogistic).
[g]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-15. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Glycidamide and Incidence of Degenerative Changes in Tibial Nerve Preparations from Male F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of Johnson et al. (1986)

	χ^2	Scaled residuals[b]				Rat blood TWA glycidamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.48	0.59	-0.25	-1.14	288.64	0.00092035	0.000463817
Logistic	0.45	0.69	-0.18	-1.21	288.87	0.00106268	0.000649044
LogLogistic[e,f]	***0.50***	***0.55***	***-0.27***	***-1.12***	***288.57***	***0.000874893***	***0.000408089***
LogProbit[e]	0.33	0.98	-0.10	-1.34	289.66	0.00123711	0.000759144
Multistage (1-degree)[g]	0.48	0.59	-0.25	-1.14	288.64	0.000920351	0.000463817
Multistage (2-degree)[g]	0.48	0.59	-0.25	-1.14	288.64	0.000920351	0.000463817
Multistage (3-degree)[g]	0.48	0.59	-0.25	-1.14	288.64	0.000920351	0.000463817
Multistage (4-degree)[g]	0.48	0.59	-0.25	-1.14	288.64	0.000920351	0.000463817
Probit	0.45	0.68	-0.19	0.68	288.84	0.00104432	0.000623954
Weibull[d]	0.48	0.59	-0.25	-1.14	288.64	0.000920351	0.000463817
						BMD_{05}	$BMDL_{05}$
LogLogistic[e,f]	***0.50***	***0.55***	***-0.27***	***-1.12***	***288.57***	***0.000414423***	***0.000193305***

[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]Rat blood TWA glycidamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Johnson et al. (1986).
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Selected model. All models provided adequate fit to the data as judged by X^2 goodness-of-fit p-value (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. BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected (LogLogistic).
[g]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-16. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Acrylamide and Incidence of Degenerative Changes in Tibial Nerve Preparations from Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of Johnson et al. (1986)

	X^2	Scaled residuals[b]				Rat blood TWA acrylamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.41	-0.01	0.00	0.98	222.69	0.00130613	0.000704889
Logistic	0.62	0.10	-0.02	0.95	220.69	0.00146511	0.00110148
LogLogistic[e]	0.41	0.00	0.00	0.98	222.69	0.00129772	0.000636942
LogProbit[e]	0.59	0.45	-0.08	-1.04	220.94	0.00154931	0.00108329
Multistage (1-degree)[f]	0.59	-0.23	0.09	1.08	220.75	0.00115579	0.000701405
Multistage (2-degree)[f]	0.41	0.00	0.00	0.99	222.68	0.00135129	0.000705558
Multistage (3-degree)[f]	0.41	0.01	0.00	1.00	222.68	0.00140517	0.000705578
Multistage (4-degree)[f]	0.41	0.01	0.00	1.00	222.68	0.00140517	0.000705578
Probit[g]	***0.62***	***0.06***	***-0.01***	***0.97***	***220.68***	***0.00141533***	***0.0010388***
Weibull[d]	0.41	-0.01	0.00	0.98	222.69	0.00131215	0.000704948
						BMD_{05}	$BMDL_{05}$
Probit[g]	***0.62***	***0.06***	***-0.01***	***0.97***	***220.68***	***0.000798991***	***0.000586137***

[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]Rat blood TWA acrylamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Johnson et al. (1986).
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models provided adequate fit to the data as judged by X^2 goodness-of-fit p-value (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. BMDLs for models providing adequate fit differed by <2–3-fold); therefore, the model with the lowest AIC was selected (Probit).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-17. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Glycidamide and Incidence of Degenerative Changes in Tibial Nerve Preparations from Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of Johnson et al. (1986)

	X^2	Scaled residuals[b]				Rat blood TWA glycidamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.41	0.00	0.00	0.98	222.69	0.000711912	0.000381903
Logistic	0.62	0.09	-0.02	0.95	220.69	0.00079139	0.000595247
LogLogistic[e]	0.41	0.00	0.00	0.98	222.69	0.000707432	0.000345627
LogProbit[e]	0.59	0.44	-0.08	-1.04	220.93	0.000836071	0.000584963
Multistage (1-degree)[f]	0.59	-0.24	0.10	1.08	220.76	0.000625365	0.00037971
Multistage (2-degree)[f]	0.41	0.00	0.00	0.99	222.68	0.000736191	0.000382278
Multistage (3-degree)[f]	0.41	0.01	0.00	1.00	222.68	0.000766549	0.000382291
Multistage (4-degree)[f]	0.41	0.01	0.00	1.00	222.68	0.000766549	0.000382291
Probit[g]	***0.62***	***0.05***	***-0.01***	***0.97***	***220.68***	***0.000764564***	***0.000561417***
Weibull[d]	0.41	-0.01	0.00	0.98	222.69	0.000715356	0.000381935
						BMD_{05}	$BMDL_{05}$
Probit[g]	***0.62***	***0.05***	***-0.01***	***0.97***	***220.68***	***0.000431712***	***0.000316857***

[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]Rat blood TWA glycidamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by Johnson et al. (1986).
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models provided adequate fit to the data as judged by X^2 goodness-of-fit p-value (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. BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected (Probit).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

In the chronic toxicity and carcinogenicity study of NTP (2011b), groups of male and female F344 rats 48/sex/group) were exposed to acrylamide in the drinking water for up to 2 years at concentrations resulting in calculated doses of 0, 0.33, 0.66, 1.32, or 2.71 mg/kg/day for the males and 0, 0.44, 0.88, 1.84, or 4.02 mg/kg/day for the females. Complete necropsies were performed on all animals that died, those that were sacrificed moribund, and those that survived to terminal sacrifice. A comprehensive set of tissues was prepared for microscopic evaluation. Special care was taken to assess neurological tissues that included brain (cerebrum, cerebellum, brain stem), sciatic nerve, and spinal cord (cervical, thoracic, lumbar).

Significantly increased incidences of axonal degeneration in the sciatic nerve of the male and female rats were observed. Table A-18 presents the incidence data for axonal degeneration in the sciatic nerves from the rats of the NTP (2011b) study.

Table A-18. Incidence Data for Axonal Degeneration in Sciatic Nerve Preparations from F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years

	Dose (mg/kg/day), males				
	0	0.33	0.66	1.32	2.71
Lesion incidence, males	5/48	7/48	7/48	11/48	23/48[a]
	Dose (mg/kg/day), females				
	0	0.44	0.88	1.84	4.02
Lesion incidence, females	4/48	348	1/48	4/48	19/48[a]

[a]Significantly ($p<0.001$) different from control incidence by Fisher's exact test performed by SRC, Inc.

Source: NTP 2011b

The chronic study of NTP (2011b) identified a NOAEL of 1.32 mg/kg/day and a LOAEL of 2.71 mg/kg/day for significantly increased incidences of axonal degeneration in the sciatic nerve of the male rats; the female rats exhibited a NOAEL of 1.84 mg/kg/day and a LOAEL of 4.02 mg/kg/day.

The PBPK model-predicted rat blood TWA acrylamide and glycidamide doses and corresponding incidence data for degenerative sciatic nerve changes in male and female F344 rats are shown in Table A-19. Benchmark modeling results from the study of NTP (2011b) using blood TWA acrylamide as the dose metric and using blood TWA glycidamide as the dose metric are presented in Tables A-20 and A-21, respectively, for the male rats, and Tables A-22 and A-23, respectively, for the female rats.

Table A-19. PBPK Model-Predicted Rat TWA Blood Acrylamide and Glycidamide Doses and Incidences of Degenerative Sciatic Nerve Changes in Male and Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years

Ingested acrylamide dose (mg/kg/day)	Rat blood TWA acrylamide dose (mM)	Rat blood TWA glycidamide dose (mM)	Number of rats	Number of rats affected
Males				
0	0	0	48	5
0.33	0.000454	0.000245	48	7
0.66	0.000912	0.000491	48	7
1.32	0.00182	0.000971	48	11
2.71	0.00377	0.00197	48	23
Females				
0	0	0	48	4
0.44	0.000540	0.000296	48	3
0.88	0.00108	0.000590	48	1
1.84	0.00226	0.00122	48	4
4.02	0.00494	0.00260	48	19

PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Source: NTP 2011b

Table A-20. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Acrylamide and Incidence of Degenerative Changes in Sciatic Nerve Preparations from Male F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of NTP (2011b)

	χ^2	Scaled residuals[b]				Rat blood TWA acrylamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.87	-0.07	-0.08	0.42	236.25	0.00156524	0.000661132
Logistic[e]	***0.98***	***-0.27***	***-0.14***	***0.35***	***234.18***	***0.00133804***	***0.00109874***
LogLogistic[f]	0.87	-0.06	-0.07	0.41	236.25	0.00157891	0.000634105
LogProbit[f]	0.84	0.04	-0.08	0.42	236.33	0.00163506	0.00104555
Multistage (1-degree)[g]	0.65	0.17	-0.66	0.72	235.64	0.00085085	0.000600222
Multistage (2-degree)[g]	0.90	-0.16	-0.07	0.37	236.17	0.00148901	0.000666046
Multistage (3-degree)[g]	0.93	-0.23	0.05	0.28	236.11	0.00148479	0.000669336
Probit	0.96	-0.31	-0.22	0.35	234.26	0.00126026	0.00102925
Weibull[d]	0.88	-0.11	-0.06	0.40	236.21	0.00154616	0.000663332
						BMD_{05}	$BMDL_{05}$
Logistic[e]	***0.98***	***-0.27***	***-0.14***	***0.35***	***234.18***	***0.000754069***	***0.000611743***

[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]Rat blood TWA acrylamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by NTP (2011b).
[d]Power restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data as judged by X^2 goodness-of-fit p-value (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. BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Logistic).
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); NTP = National Toxicology Program; PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-21. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Glycidamide and Incidence of Degenerative Changes in Sciatic Nerve Preparations from Male F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of NTP (2011b)

Model	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMD	Dose above BMD	Overall largest	AIC	Rat blood TWA glycidamide dose (mM)[c] BMD_{10}	$BMDL_{10}$
Gamma[d]	0.86	-0.06	-0.08	0.42	236.26	0.000841019	0.000352709
Logistic[e]	***0.97***	***-0.28***	***-0.17***	***0.35***	***234.21***	***0.000702251***	***0.00057741***
LogLogistic[f]	0.87	-0.05	-0.07	0.42	236.25	0.000847186	0.000344671
LogProbit[f]	0.83	0.05	-0.08	0.42	236.33	0.000876216	0.000552102
Multistage (1-degree)[g]	0.62	0.16	-0.72	0.76	235.77	0.000448601	0.000316751
Multistage (2-degree)[g]	0.90	-0.16	-0.09	0.34	236.18	0.000796366	0.000355351
Multistage (≥3-degree)[g]	0.93	-0.23	0.05	0.29	236.11	0.000796521	0.000357633
Probit	0.95	-0.32	-0.26	0.36	234.30	0.000661509	0.000540898
Weibull[d]	0.88	-0.10	-0.06	0.41	236.22	0.000829981	0.000354012
						BMD_{05}	$BMDL_{05}$
Logistic[e]	***0.97***	***-0.28***	***-0.17***	***0.35***	***234.21***	***0.000396239***	***0.000321782***

[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]Rat blood TWA glycidamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by NTP (2011b).
[d]Power restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data as judged by X^2 goodness-of-fit p-value (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. BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Logistic).
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); NTP = National Toxicology Program; PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-22. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Acrylamide and Incidence of Degenerative Changes in Sciatic Nerve Preparations from Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of NTP (2011b)

	χ^2	Scaled residuals[b]				Rat blood TWA acrylamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.39	0.09	-0.01	0.81	159.83	0.00322124	0.00229724
Logistic	0.16	-0.78	0.37	1.63	160.82	0.00249874	0.00208354
LogLogistic[e]	0.39	0.13	-0.01	0.80	159.86	0.00330861	0.00229704
LogProbit[e]	0.39	0.05	-0.01	0.83	159.80	0.00311592	0.0022417
Multistage (1-degree)[f]	0.01	-1.83	-1.45	-1.83	167.54	0.00180843	0.00123452
Multistage (2-degree)[f]	0.26	-0.86	0.52	-1.26	160.06	0.00254487	0.00201577
Multistage (3-degree)[f,g]	**0.54**	**-0.22**	**0.09**	**0.92**	**158.11**	**0.00307014**	**0.00228873**
Multistage (4-degree)[f]	0.39	0.20	-0.02	0.78	159.88	0.00343689	0.00232663
Probit	0.11	-0.94	0.52	1.69	161.63	0.00233731	0.00192611
Weibull[d]	0.39	0.15	-0.01	0.80	159.88	0.00338563	0.00232739
						BMD_{05}	$BMDL_{05}$
Multistage (3-degree)[f,g]	**0.54**	***-0.22***	***0.09***	***0.92***	***158.11***	***0.0024152***	***0.00154042***

[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]Rat blood TWA acrylamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by NTP (2011b).
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models except the Multistage 1-degree provided adequate fit to the data (X^2 goodness-of-fit p-value >0.1). BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Multistage 3-degree).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); NTP = National Toxicology Program; PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

Table A-23. Benchmark Results for PBPK Model-Predicted Rat Blood TWA Glycidamide and Incidence of Degenerative Changes in Sciatic Nerve Preparations from Female F344 Rats Administered Acrylamide in the Drinking Water for up to 2 Years in the Study of NTP (2011b)

	χ^2	Scaled residuals[b]				Rat blood TWA glycidamide dose (mM)[c]	
Model	Goodness of fit p-value[a]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{10}	$BMDL_{10}$
Gamma[d]	0.39	0.09	-0.01	-1.08	159.82	0.00171592	0.00123645
Logistic	0.15	-0.82	0.39	1.67	161.02	0.00132224	0.00110363
LogLogistic[e]	0.39	0.12	-0.01	-1.09	159.86	0.00176227	0.00123714
LogProbit[e]	0.40	0.04	-0.01	-1.06	159.79	0.00166352	0.00120814
Multistage (1-degree)[f]	0.01	-1.85	-1.47	-1.85	167.89	0.000966702	0.000659626
Multistage (2-degree)[f]	0.24	-0.91	0.56	-1.28	160.29	0.00134688	0.00107179
Multistage (3-degree)[f]	0.52	-0.27	0.11	-1.10	158.17	0.00161831	0.00122539
Multistage (4-degree)[f,g]	***0.59***	***0.16***	***-0.01***	***-1.10***	***157.88***	***0.00181181***	***0.00125584***
Probit	0.10	-0.98	0.56	1.72	161.87	0.00123781	0.00102087
Weibull[d]	0.39	0.14	-0.01	-1.10	159.87	0.00180181	0.00125287
						BMD_{05}	$BMDL_{05}$
Multistage (4-degree)[f,g]	***0.59***	***0.16***	***-0.01***	***-1.10***	***157.88***	***0.00151342***	***0.000860953***

[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]Rat blood TWA glycidamide doses predicted by the PBPK model of Sweeney et al. (2010) based on oral doses estimated by NTP (2011b).
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models except the Multistage 1-degree provided adequate fit to the data (X^2 goodness-of-fit p-value >0.1). BMDLs for models providing adequate fit differed by <2–3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (Multistage 4-degree).

AIC = Akaike's Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: e.g., $_{10}$ = exposure concentration associated with 10% extra risk); NTP = National Toxicology Program; PBPK = physiologically based pharmacokinetic; TWA = time-weighted average

The best-fitting model results for incidence of light microscope-detected degenerative peripheral nerve changes in the male and female F344 rats from the studies of Johnson et al. (1986) and NTP (2011b) using rat blood TWA acrylamide as the dose metric and rat blood TWA glycidamide as the dose metric are presented in Table A-24 for comparison. The human PBPK model (Sweeney et al. 2010) model was used to predict the daily human equivalent dose (HED in mg/kg/day) corresponding to the 95% lower confidence limit ($BMDL_{10}$ and $BMDL_{05}$) on the BMD_{10} and BMD_{05} associated with the rat PBPK model-predicted blood TWA acrylamide dose and rat PBPK model-predicted blood TWA glycidamide dose. The corresponding rat external doses and HEDs are also shown in Table A-24.

Table A-24. Summary of BMDL Values and Corresponding Rat External Doses and HEDs from the Best-Fitting Models for Incidences of Degenerative Changes in Peripheral Nerves Using Rat PBPK Model-Predicted Blood TWA Acrylamide as the Dose Metric and Glycidamide as the Dose Metric for the Male and Female F344 Rats from the Chronic Studies of Johnson et al. (1986) and NTP (2011b)

Parameter	Rat blood TWA acrylamide-based BMDL (mM)	Rat dose[a] (mg/kg/day)	HED (mg/kg/day)	Rat blood TWA glycidamide-based BMDL (mM)	Rat dose[a] (mg/kg/day)	HED (mg/kg/day)
Johnson et al. (1986) study						
Male rat $BMDL_{10}$	0.000774339	0.57	0.13	0.000408089	0.56	0.77
Female rat $BMDL_{10}$	0.0010388	0.88	0.18	0.000561417	0.86	1.07
Male rat $BMDL_{05}$	0.000366792	0.23	0.063	0.000193305	0.26	0.36
Female rat $BMDL_{05}$	0.000586137	0.50	0.10	0.000316857	0.49	0.59
NTP (2011b) study						
Male rat $BMDL_{10}$	0.00109874	0.80	0.19	0.00057741	0.78	1.10
Female rat $BMDL_{10}$	0.00228873	1.86	0.39	0.00125584	1.89	2.53
Male rat $BMDL_{05}$	0.000611743	0.44	0.11	0.000302968	0.41	0.57
Female rat $BMDL_{05}$	0.00154042	1.26	0.27	0.000860953	1.29	1.68

[a]Rat dose is the PBPK model-predicted dose of acrylamide corresponding to the PBPK model-predicted HED at the BMD-predicted rat blood TWA acrylamide- or glycidamide-based BMDL.

BMDL = 95% lower confidence limit on the benchmark dose (BMD) which is the maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; (subscripts denote benchmark response: e.g., $_{05}$ = exposure concentration associated with 5% extra risk); HED = human equivalent dose; NTP = National Toxicology Program; TWA = time-weighted average

Figure A-8 shows the plotted results from the best-fitting model (Log-logistic; Table A-14) for PBPK model-predicted blood TWA acrylamide and degenerative tibial nerve changes in the male rats from the study of Johnson et al. (1986) using a BMR of 5% extra risk.

Figure A-8. Fit of Logistic Model to Data on the Incidence of Degenerative Tibial Nerve Changes in Male F344 Rats Exposed to Acrylamide in the Drinking Water for up to 2 Years Using Time-Weighted Average Acrylamide Blood Dose (mM) as the Dose Metric and a Benchmark Response of 5% Extra Risk in the Study of Johnson et al. (1986)

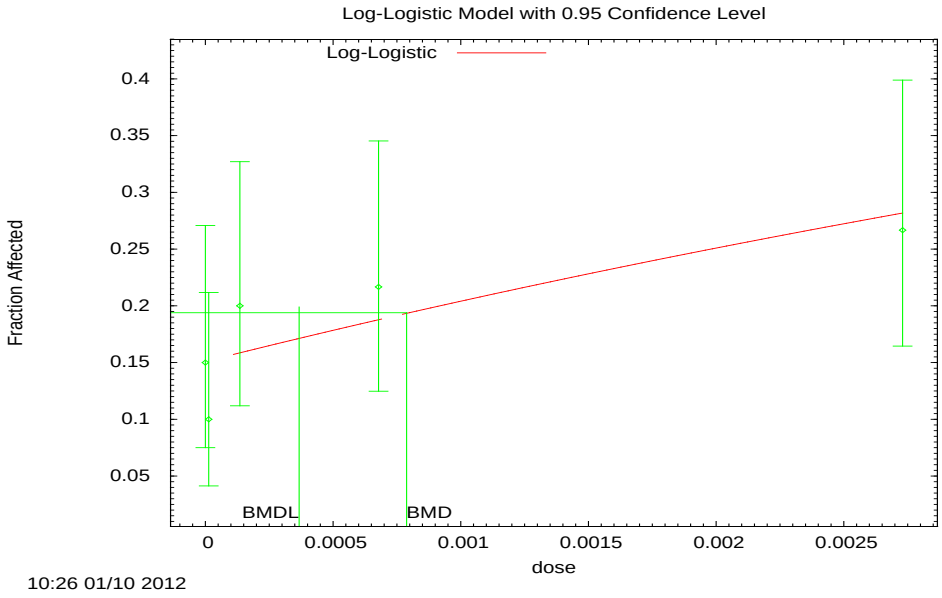
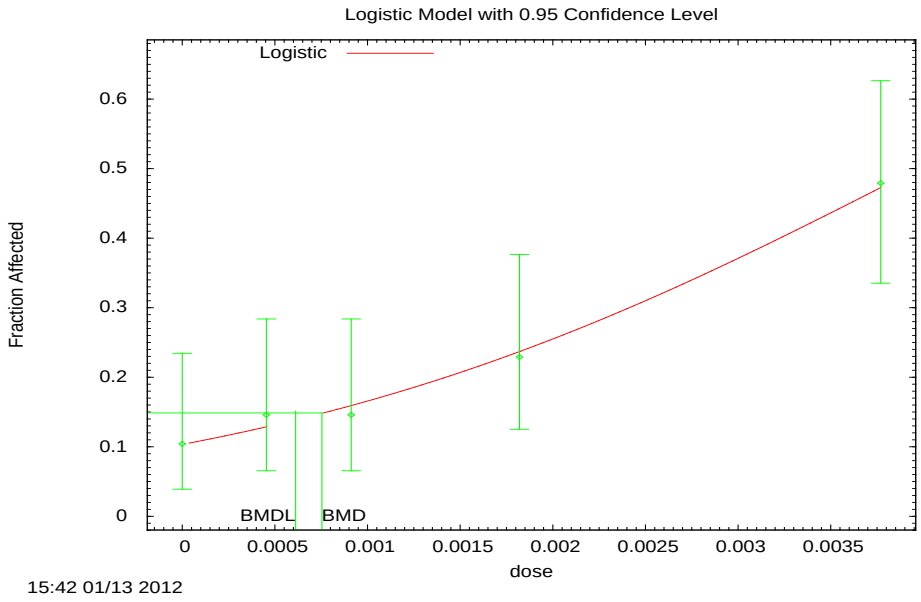


Figure A-9 shows the plotted results from the best-fitting model (Logistic; Table A-20) for PBPK model-predicted blood TWA acrylamide and degenerative sciatic nerve changes in the male rats from the study of NTP (2011b) using a BMR of 5% extra risk.

Figure A-9. Fit of Log-logistic Model to Data on the Incidence of Degenerative Sciatic Nerve Changes in Male F344 Rats Exposed to Acrylamide in the Drinking Water for up to 2 Years Using Time-Weighted Average Acrylamide Blood Dose (mM) as the Dose Metric and a Benchmark Response of 5% Extra Risk in NTP (2011b)



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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

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

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

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

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

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

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

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

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

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

LEGEND

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

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

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

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

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

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

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

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

in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

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

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

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

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

LEGEND

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

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

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

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

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

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

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

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

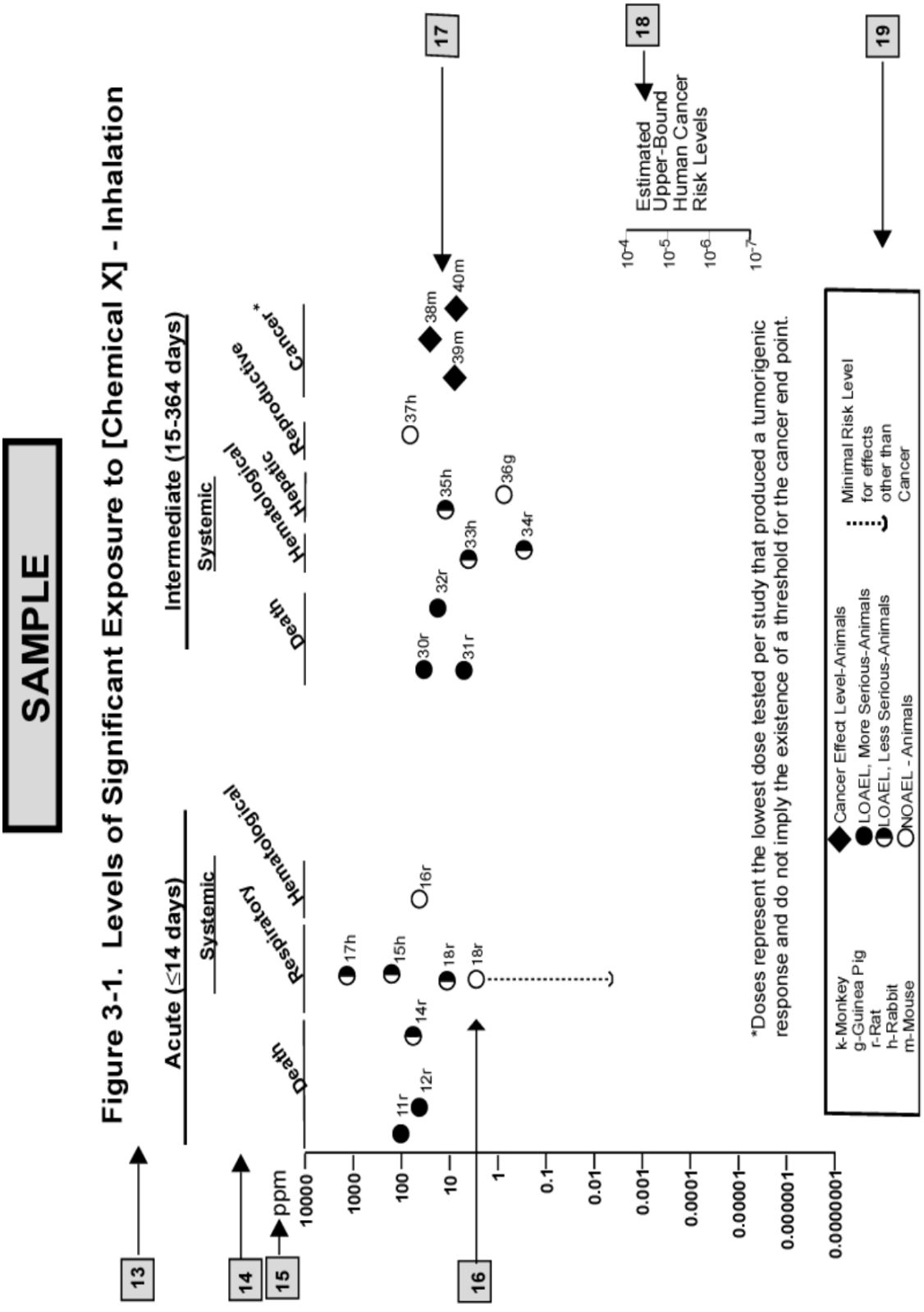
(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

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

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
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
Acute (≤14 days)
Intermediate (15-364 days)
Systemic
Respiratory
Hematological
Death
Hepatic
Reproductive
Cancer *
ppm
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
11r
12r
14r
15h
16r
17h
18r
18r
30r
31r
32r
33h
34r
35h
36g
37h
38m
39m
40m
Estimated Upper-Bound Human Cancer Risk Levels
10^{-4}
10^{-5}
10^{-6}
10^{-7}
*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.
k-Monkey
g-Guinea Pig
r-Rat
h-Rabbit
m-Mouse
Cancer Effect Level-Animals
LOAEL, More Serious-Animals
LOAEL, Less Serious-Animals
NOAEL - Animals
Minimal Risk Level for effects other than Cancer
13
14
15
16
17
18
19

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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/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
EH	epoxide hydrolase
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
GST	glutathione S-transferase
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