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Provisional Peer-Reviewed Toxicity Values for

Acrylic Acid
(CASRN 79-10-7)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ACRYLIC ACID (CASRN 79-10-7)

BACKGROUND

HISTORY

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR);
   - California Environmental Protection Agency (CalEPA) values; and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by a panel of six EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

Both RfD and RfC values are available for acrylic acid (chemical structure shown in Figure 1) on IRIS (U.S. EPA, 2009a). The RfD of 0.5 mg/kg-day is based on a NOAEL of 53 mg/kg-day and a LOAEL of 240 mg/kg-day for reduced pup weight in a two-generation reproductive study of rats exposed to acrylic acid in drinking water (BASF, 1993, later published as Hellwig et al., 1997). The RfC of 0.001 mg/m^3 is based on a LOAEL of 14.94 mg/m^3 ($LOAEL_{HEC}$ = 0.33 mg/m^3) for degeneration of the nasal olfactory epithelium in a subchronic mouse inhalation study (Miller et al., 1981). Both assessments were posted on 2/17/94, and neither was cited to a source document. The HEAST (U.S. EPA, 1997) lists a subchronic RfD of 0.5 mg/kg-day and a subchronic RfC of 0.003 mg/m^3. These subchronic values are based on the same studies, critical effects, and critical effect levels as the chronic values on IRIS (U.S. EPA, 2009a). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) includes a Health and Environmental Effects Profile (HEEP) for acrylic acid (U.S. EPA, 1984) that did not attempt quantitative assessment due to inadequate data. Acrylic acid is not on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). The Agency for Toxic Substances and Disease Registry (ATSDR, 2009) has not prepared a toxicological profile for acrylic acid. The World Health Organization (WHO, 1997) developed an Environmental Health Criteria document for acrylic acid and lists guidance values of 0.054 mg/m^3 for inhalation exposure and 9.9 mg/L for drinking water (associated with a Tolerable Intake [TI] value of 3.1 mg/kg-day). The drinking water value is based on a NOAEL of 78 mg/kg-day from a chronic rat study (Hellwig et al., 1993), and the inhalation value is based on the LOAEL of 15 mg/m^3 from the above-mentioned subchronic mouse study (Miller et al., 1981). The California Environmental Protection Agency (CalEPA, 2009a,b) has not derived values for longer-term exposure to acrylic acid.

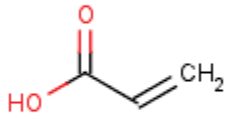

Figure 1. Chemical Structure of Acrylic Acid

The American Conference of Governmental Industrial Hygienists (ACGIH, 2008) lists a threshold limit value (TLV) for acrylic acid of 2 ppm as an 8-hour time-weighted average (TWA) to prevent upper respiratory tract irritation. The National Institute of Occupational Safety and Health (NIOSH, 2008) recommended exposure level (REL) is also 2 ppm (6 mg/m^3). The Occupational Safety and Health Administration (OSHA, 2009) has not derived occupational exposure limits for acrylic acid. Interim Acute Exposure Guidelines (AEGL) ranging from 1.5 ppm (AEGL1, 10 minutes to 8 hours) to 480 ppm (AEGL3, 10 minutes) were derived for acrylic acid in 2003 (U.S. EPA, 2009b). CalEPA (2009b) has derived an acute 1-hour REL of 6 mg/m^3 for acrylic acid on the basis of respiratory irritation in rabbits, and it lists eyes and respiratory tract as target organs.

A cancer assessment for acrylic acid is not available on IRIS (U.S. EPA, 2009a) or in the HEAST (U.S. EPA, 1997). No assessment of the carcinogenic potential of acrylic acid has been made in the HEEP (U.S. EPA, 1984) due to the lack of relevant studies. The International Agency for Research on Cancer (IARC, 1999, 1987, 1979) lists acrylic acid as Group 3 (not classifiable) with regard to carcinogenic potential in humans because of the lack of relevant data for humans or animals. Acrylic acid is not included in the 11th Report on Carcinogens (National Toxicology Program [NTP], 2005) and has not been studied for carcinogenicity by NTP (2009). CalEPA (2009b) has not prepared a quantitative estimate of carcinogenic potential for acrylic acid.

Literature searches were conducted from 1960s through October 2009 for studies relevant to the derivation of provisional toxicity values for acrylic acid. Databases searched include MEDLINE, TOXLINE (with NTIS), BIOSIS, TSCATS/TSCATS2, CCRIS, DART, GENETOX, HSDB, RTECS, Chemical Abstracts, and Current Contents (last 6 months).

REVIEW OF PERTINENT DATA

HUMAN STUDIES

Schwartz et al. (1989) studied olfactory function in chemical workers exposed to vapors of acrylic acid and other acrylates and methacrylates at a large manufacturing facility. The study population included 731 (618 males and 113 females, mean age = 42.9 ± 11.3 years). Workers

filled out questionnaires including medical history and history of smell or taste dysfunction, and self-administered the University of Pennsylvania Smell Identification test (UPSIT) to assess olfactory function. Cross-sectional (prevalence) and nested case-control studies were performed. For the cross-sectional study, workers were categorized according to current exposure based on job title: no chemical exposure (n = 319), exposure to chemicals other than acrylic acid, acrylates, and methacrylates (n = 193), exposure to lower levels of acrylic acid, acrylates, and methacrylates (n = 164), and exposure to higher levels of acrylic acid, acrylates, and methacrylates (n = 55). UPSIT scores did not differ significantly across groups, with or without control for age, ethnicity, and smoking status as potential confounders. The case-control study was limited to workers who had been full-time employees at the plant for at least 6 months. Cases (n = 77) were selected as subjects scoring at or below the 10th percentile (for their age) on the UPSIT. Controls were matched 1:1 based on age, ethnicity, and gender. Cumulative exposure scores were calculated for cases based on job history. Odds ratios (ORs) were significantly increased for all workers, and, in particular, for workers who had never smoked, with or without adjustment for multiple confounders (adjusted OR = 2.8 [1.1, 7.0] for all workers and 13.5 [2.1, 87.6] for non smokers). ORs (crude or adjusted) increased with cumulative exposure score. The results of the case-control study suggest an effect of acrylic acid, acrylates, and methacrylates on olfactory function, but they cannot distinguish which of the chemicals may have contributed to the observed effect.

Tucek et al. (2002) performed a prospective cohort study with an 8-year follow-up of workers exposed to acrylic acid and many other chemicals in the production of acrylic acid and its esters. The study cohort included 60 workers occupationally exposed to acrylic acid, its esters, and other chemicals at a single facility in the Czech Republic for at least 5 years (mean = 13 ± 5 years). Controls were 60 unexposed workers from the same plant. Mean subject age was 40 ± 8 years for both groups. Exposure was measured at 15 workstations for selected chemicals only (acrylic acid was not included) using personal passive dosimeters at regular intervals. Health status of workers was assessed annually by general medical examination, hematology, serum chemistry, urinalysis, serum immunology, selected tumor markers, and spirometry. The study found no evidence of health-related changes in exposed workers that could be related to exposure.

ANIMAL STUDIES

Throughout the discussion that follows, use of the term "significantly" refers to a statistically significant deviation from controls.

Oral Exposure

Subchronic Studies—Fisher 344 rats (15/sex/group) were administered acrylic acid (≈97% pure) in drinking water at target doses of 0, 83, 250, or 750 mg/kg-day for 3 months (DePass et al., 1983). Food and drinking water consumption and body weight were measured weekly. Serum chemistry (cholesterol, glucose, urea nitrogen [BUN], alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and creatine phosphokinase [CPK]), hematology (hemoglobin [Hgb], hematocrit [Hct], red blood cell count [RBC], white blood cell count [WBC], and reticulocyte count), and urinalysis (specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood, and nitrite) were evaluated approximately 2 weeks prior to sacrifice. All test animals received gross pathological examination upon sacrifice at the end of the treatment period, including measurement of relative and absolute

weights of the liver, kidney, heart, spleen, brain, and testes. Microscopic examination of the following organs and tissues was conducted for control and high-dose animals: pituitary, thyroid, parathyroids, adrenals, heart, thymus, spleen, mesenteric lymph node, nasal cavity, trachea, lungs, ovaries and oviducts, kidneys, urinary bladder, tongue, esophagus, stomach, duodenum, colon, liver, pancreas, brain, eyes, skin, mammary gland, and sternum. Only organs with gross lesions were examined microscopically in low- and mid-dose rats.

No mortality or clinical signs of toxicity were observed (DePass et al., 1983). As shown in Table 1, mean body-weight gain was significantly reduced in high-dose males (-30%) and mid- (-12%) and high-dose (-39%) females in comparison with controls. Food consumption was significantly reduced in high-dose animals throughout the study. Water consumption was significantly reduced in all treated male groups and in mid- and high-dose females. Changes in organ weights appeared to occur in parallel to decreased body-weight gain (see Table 1). As shown in Table 2, some minor changes in serum chemistry were also noted in mid- and high-dose animals. There were no effects on hematological variables (data not shown). Based on DePass et al. (1983), an increase in blood urea nitrogen (BUN) was observed for high-level dose in male rats. In the female, a decrease in serum cholesterol and increases in BUN, glucose, and alkaline phosphatase and aspartate transaminase were observed among the high dose levels. Increases in BUN and alkaline phosphatase were dose related. The authors did not present additional information on statistical significance or conclusions. Urinalysis revealed increased urinary protein levels in the mid- and high-dose rats of both sexes (data not shown) and decreased urinary pH in the high-dose females (median = 6.0 versus 7.0 in controls). No gross or microscopic lesions were detected. The LOAEL for this study is 250 mg/kg-day based on reduced body-weight gain in females. Other changes at this dose level included minor changes in organ weights, serum chemistry, and urinalysis that may have been secondary to the effect on body weight. In addition, DePass et al. (1983) reported that at 83 mg/kg-day the only effect was a reduction of water consumption by male rats. There was no significant treatment related to histopathologic changes. Many effects observed may have been the results of decreased water consumption rather than specific toxic effect of acrylic acid. Organ weight effects in male rats include significant reduction in absolute liver weight observed at high dose level. Other statistically significant organ weight changes at the two lower dosage were probable chance occurrences unrelated to treatment. The NOAEL for the study is 83 mg/kg-day.

Hellwig et al. (1993) performed gavage and drinking water studies with acrylic acid in rats. In the gavage study, Wistar rats (10/sex/group) were administered acrylic acid (99% pure stabilized with 200-ppm hydroquinine monomethylether) in water by gavage at doses of 0, 150, or 375 mg/kg-day, 5 days/week, for 3 months. Body weight, food consumption, and drinking water consumption were determined once per week. Animals were examined daily for clinical signs of toxicity. All test animals received a gross pathological examination, which included measurement of relative and absolute weights of the liver, kidney, spleen, testes, ovaries, adrenals, and brain. Histopathological examination was made for gross lesions and tissues from the esophagus, stomach, small intestine, liver, kidneys, urinary bladder, adrenals, tongue, and buccal and nasal mucosa. The study authors reported slight-to-moderate retardation of growth in high-dose males and indications of an effect on growth in high-dose females as well during the first 3 weeks of the study (data not shown). Hellwig et al. (1993) presents results of the hematological and urinanalytical examinations (Table 2 and Table 3 in the original article) at

Table 1. Summary of Changes in Body and Organ Weights in a 90-Day Drinking Water Study of Rats Exposed to Acrylic Acid[a]

	Dose (mg/kg-day)							
	0		83		250		750	
Endpoint/Sex	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Male								
Diet consumption (g/kg-day)	16.9	0.6	16.4	0.9	16.2	0.6	14.0[d]	0.6
Water consumption (mL/rat-day)	21.4	0.7	19.4[c]	1.3	17.5[d]	0.8	13.0[d]	0.7
Body-weight gain (g)	200.6	20.2	196.7	17.3	188.2	23.5	141.5[d]	21.5
Liver absolute (g)	11.08	0.89	11.17	0.85	11.30	1.64	9.33[d]	1.25
Liver relative (%)	3.40	0.14	3.50	1.15	3.61	0.38	3.52[b]	0.15
Kidney absolute (g)	2.15	0.13	2.14	0.16	2.20	0.18	2.06	0.22
Kidney relative (%)	0.66	0.02	0.67	0.03	0.71[d]	0.03	0.78[d]	0.04
Spleen absolute (g)	0.60	0.06	0.61	0.06	0.60	0.08	0.53[c]	0.05
Spleen relative (%)	0.18	0.01	0.19	0.02	0.19	0.02	0.20[c]	0.02
Heart absolute (g)	0.82	0.10	0.83	0.08	0.81	0.10	0.71[c]	0.09
Heart relative (%)	0.25	0.03	0.26	0.02	0.26	0.02	0.27	0.02
Brain absolute (g)	1.84	0.06	1.81	0.08	1.81	0.08	1.74[c]	0.08
Brain relative (%)	0.57	0.03	0.57	0.03	0.58	0.04	0.66[d]	0.05
Testes absolute (g)	2.72	0.32	2.73	0.14	2.82	0.14	2.72	0.17
Testes relative (%)	0.84	0.11	0.86	0.07	0.91[d]	0.07	1.04[d]	0.06
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Female								
Diet consumption (g/kg-day)	10.4	0.4	10.6	0.2	10.2	0.6	8.7[c]	0.3
Water consumption (mL/rat-day)	15.0	0.7	14.9	0.8	11.8[d]	0.7	8.6[d]	0.5
Body-weight gain (g)	78.0	10.8	82.1	11.1	68.4[b]	9.8	48.0[d]	8.2
Liver absolute (g)	5.70	0.45	5.84	0.57	5.61	0.47	4.91[d]	0.50
Liver relative (%)	3.19	0.13	3.16	0.14	3.29	0.18	3.27	0.22
Kidney absolute (g)	1.24	0.08	1.29	0.08	1.37[d]	0.07	1.34[c]	0.10
Kidney relative (%)	0.69	0.03	0.70	0.04	0.80[d]	0.06	0.89[d]	0.04
Spleen absolute (g)	0.43	0.05	0.46	0.05	0.43	0.04	0.37[d]	0.04
Spleen relative (%)	0.24	0.02	0.25	0.02	0.25	0.02	0.24	0.02
Heart absolute (g)	0.54	0.07	0.55	0.06	0.54	0.05	0.45[d]	0.04
Heart relative (%)	0.30	0.03	0.30	0.02	0.32	0.02	0.30	0.02
Brain absolute (g)	1.65	0.14	1.66	0.10	1.68	0.08	1.61	0.12
Brain relative (%)	0.93	0.10	0.90	0.08	0.99	0.08	1.07[d]	0.09

[a]DePass et al. (1983)
[b]$p < 0.05$
[c]$p < 0.01$
[d]$p < 0.001$

Table 2. Clinical Chemistry Values in Rats Exposed to Acrylic Acid in Drinking Water for 90 Days[a]

Dose (mg/kg-day)	Endpoint (Mean ± SD)						
	Cholesterol (mg/dL)	BUN (mg/dL)	Glucose (mg/dL)	ALP (Units/L)	AST (Units/L)	ALT (Units/L)	CPK (Units/L)
Male							
0	53 ± 7.9	16 ± 3.1	114 ± 10.2	103 ± 8.60	62 ± 8.5	28 ± 4.6	98 ± 34
83	56 ± 6.5	16 ± 2.6	118 ± 10.7	103 ± 6.50	58 ± 6.5	28 ± 5.4	103 ± 41.8
250	54 ± 8.0	16 ± 1.8	111 ± 10.7	103 ± 7.80	58 ± 6.8	28 ± 4.4	91 ± 29
750	60 ± 7.9	19 ± 3.8[c]	115 ± 9.00	102 ± 10.5	62 ± 9.8	32 ± 4.9	134 ± 120
Female							
0	77 ± 10	16 ± 2.5	100 ± 8.70	71 ± 11	54 ± 6.6	22 ± 2.1	67 ± 21
83	76 ± 7.9	17 ± 2.0	107 ± 6.00	73 ± 10	54 ± 5.4	21 ± 2.3	60 ± 25
250	68 ± 7.0[c]	19 ± 2.8[c]	105 ± 7.60	80 ± 13[b]	62 ± 14	23 ± 4.1	148 ± 163
750	55 ± 6.2[d]	24 ± 3.3[d]	109 ± 11.3[b]	85 ± 7.6[d]	60 ± 7.1[b]	24 ± 3.8	88 ± 59

[a]DePass et al. (1983)
[b]$p < 0.05$
[c]$p < 0.01$
[d]$p < 0.001$

various intervals did not indicate an obvious treatement-related pattern in any of the clino-chemical, hematological or urinanalytical parameters monitored. Also, reports that the differences were marginal, inconsistent or lacked a dose-effect relationship. Clinical signs observed in most animals in both dose groups from 3 weeks onward included tympanites (abdominal swelling) of the gastrointestinal tract, cyanosis, and dyspnea (shortness of breath). Mortality occurred in 10/20 animals (5 males and 5 females) in the low-dose group and 15/20 animals (6 males, 9 females) in the high-dose group. The timing of mortality and clinical signs specifically associated with animals that died were not discussed. Pathological examinations revealed irritation in the forestomach and glandular stomach and purulent catarrhal rhinitis as prominent effects of gavage treatment with acrylic acid. Necrotizing tubular nephrosis was observed in most of the animals that died during the study. Table 3 summarizes the incidences of these endpoints. Statistical analyses are not reported for the results of gross or microscopic examinations. No results or conclusions regarding organ weights are reported. The lowest dose tested in this study, 150 mg/kg-day, is a FEL based on increased mortality.

Concurrent with the gavage study described above, the same researchers conducted a 12-month drinking water study that included a satellite group that was sacrificed after 3 months of exposure (Hellwig et al., 1993). Wistar rats (20/sex/group for the main group and 10/sex/group for the satellite groups) were administered acrylic acid (99% pure stabilized with 200-ppm hydroquinine monomethylether) in drinking water at concentrations of 0, 120, 800, 2000, or 5000 ppm (equivalent to mean measured doses of 0, 9, 61, 140, or 331 mg/kg-day) for 3 months (satellite group) or 12 months (main group) (Hellwig et al., 1993). Food and drinking water consumption and body weight were measured once per week, and animals were examined daily for clinical signs of toxicity. Serum chemistries, hematological analyses, and urinalysis

Table 3. Histological Findings in Rats Exposed to Acrylic Acid via Gavage for 3 Months[a]

	Number of Rats with Lesions					
	0 (controls)		150 mg/kg-day		375 mg/kg-day	
Site and Lesion	**Males**	**Females**	**Males**	**Females**	**Males**	**Females**
Stomach						
Hyperemia of the mucosal apices	0	0	3	1	5	3
Erosion in glandular stomach without cellular reaction	0	0	2	1	2	4
Subepithelial edema (forestomach), especially in the region of the *plica marginata*	0	0	0	1	3	0
Epithelial hyperplasia (forestomach), especially in the region of the *plica marginata*	0	0	1	1	3	1
Esophagus						
Purulent mucus, intraluminal	0	0	0	0	0	1
Nasal cavity						
Purulent catarrhal exudate	0	0	5	7	6	7
Mucosal atrophy/metaplasia	0	0	0	1	1	1
Pharyngeal duct						
Purulent catarrhal exudate	0	0	5	6	6	6
Mucosal atrophy/metaplasia	0	0	2	5	5	5
Sinus maxillaries						
Purulent catarrhal exudate	0	0	2	1	2	3
Kidneys						
Ballooning degeneration/ fragmentation/necrosis of tubular cells (cortex)	0	0	5	4	5	7

[a]Hellwig et al. (1993)

were conducted on Weeks 4, 12, 26, and 51. All test animals received gross pathological examination, which included measurement of body weight and relative and absolute weights of the liver, kidney, spleen, testes, ovaries, adrenals, and brain. Histopathological examinations were performed on all gross lesions. In the satellite groups, histopathological examinations were conducted for controls and the two highest-dose groups, and they included examination of the esophagus, stomach, small intestine, urinary bladder, adrenals, tongue, buccal mucosa, and nasal mucosa. For the main groups, histopathological examinations were conducted for the liver and kidneys of all animals in all test groups, and on a comprehensive list of tissues and organs for controls and the two highest-dose groups.

No treatment-related mortality was observed in this study; the only death was a low-dose male (Hellwig et al., 1993). Drinking water consumption was significantly reduced (-15 to 20% relative to controls) in high-dose (331 mg/kg-day) males throughout the study and in 140-mg/kg-day males (-10% relative to controls) for the first 14 weeks of the study, suggesting that palatability was an issue. Body-weight gain was reduced as well in high-dose males; the

difference in body weight from controls ranged from 6–8% for most of the study. Neither drinking water consumption nor body-weight gain differed from controls in treated females. There were sporadic statistically significant ($p < 0.05$) changes between controls and rats exposed to acrylic acid with regard to some hematological and urinalysis variables, but the changes were marginal and were not consistent over time or dose-related. There were no effects on serum chemistry (data not shown). In contrast with the 3-month gavage study, the histopathology data showed no statistically significant treatment-related differences between controls and animals exposed to acrylic acid at any dose, at either the 3-month or 12-month sacrifices, suggesting that the effects observed in the gavage studies were due to irritation associated with bolus doses. Because the small change in body weight observed in high-dose males in this study is not considered biologically significant, the NOAEL for this study is 331 mg/kg-day (highest dose tested).

Chronic Studies—Wistar rats (50/sex/group) were administered acrylic acid (99% pure stabilized with 200-ppm hydroquinine monomethylether) in drinking water at concentrations of 0, 120, 400, or 1200 ppm for 26 (males) or 28 (females) months (Hellwig et al., 1993). Based on measured body weight and drinking water consumption, these concentrations are equivalent to doses of 0, 8, 27, or 78 mg/kg-day. For the first 3 months of the study, body weight and drinking water consumption were determined once per week. Body weight was then determined once every 4 weeks, and drinking water consumption was determined once every 3 months. General well-being of the animals was checked daily. Hematological variables were assessed following 12, 18, 26 (males), and 28 (females) months of exposure. All test animals received gross pathological examination, including the measurement of body weights, and relative and absolute weights of the liver, kidney, spleen, testes, ovaries, adrenals, and brain. Histopathological examinations were performed on a comprehensive list of tissues and organs, including sections from bone marrow (femur), vagina, coagulation gland, mandibular lymph node, tongue, and buccal mucosa.

No treatment-related mortality or clinical signs of toxicity were observed (Hellwig et al., 1993). There were no significant treatment-related effects on body weight or water consumption. Hematology data showed no consistent and dose-related effects. No significant gross pathological changes were observed. A slight increase in the incidence of hepatocellular fatty deposits was observed in high-dose males (incidences of 5/50, 6/49, 6/50, and 13/50) but not in females. This effect is not considered to be toxicologically relevant due to the low incidence, lack of statistical significance, and the lack of histopathological alterations of the liver in other studies (DePass et al., 1983). The histopathology data showed no other significant treatment-related nonneoplastic or neoplastic findings. Based on these findings, the NOAEL for this study is 78 mg/kg-day (highest dose tested).

Reproductive/Developmental Studies—In a two-generation reproductive study (Hellwig et al., 1997), acrylic acid (98.9% pure) was administered in drinking water at concentrations of 0, 500, 2500, or 5000 ppm to groups of 25 male and 25 female Wistar rats (35 days old at the beginning of treatment). After at least 70 days of treatment, the F_0 parental-generation animals were mated within the dose groups to produce one litter. Litters were culled to eight pups at Day 4 postparturition, and groups of 25 male and female F_1 pups were selected for the F_1 parental generation and were mated after at least 98 days of treatment. F_2 litters were culled to eight pups and were raised to Day 21 postpartum. Acrylic acid treatment was continuous throughout the premating, gestational, and lactational periods. Pups from both

generations were necropsied at Days 4 and 21 postpartum. In addition to body weight, food, and water consumption and general reproductive parameters, pups were monitored for behavior and developmental milestones, and some pups were examined for visceral and skeletal abnormalities. Other endpoints that were monitored include nesting, littering and lactation behavior, gripping reflex, hearing startle reflex, pupillary reflex, pinna unfolding, auditory canal opening, and eye opening.

The acrylic acid doses based on water intake were estimated to be 53, 240, and 460 mg/kg-day in the animals receiving 500, 2500, and 5000 ppm in drinking water, respectively (Hellwig et al., 1997). A consistent finding throughout the study was decreased water consumption at the two highest doses. Water consumption was reduced 11–14% at 460 mg/kg-day in the F_0 parental animals compared with controls throughout premating, gestation, and lactation but was not reduced in F_0 animals receiving 240 mg/kg-day. Statistically significant decreases in body weight were observed in F_0 males receiving 460 mg/kg-day during Study Weeks 12 through 20, but these changes were not large enough to be considered biologically relevant (i.e., 6–7% less than control values; a decrease of 10% is typically considered to be adverse). The body weights among F_0 females were unaffected by treatment. High-dose male and female F_1 parents had significantly lower body weights than controls (13–26% less in males and 11–23% less in females) throughout the entire 23-week period. Water consumption was consistently and significantly reduced in F_1 male and female parents exposed to 240 or 460 mg/kg-day. No changes in water consumption or body weight were observed in F_0 or F_1 parents exposed to 53 mg/kg-day. Pups of both generations exposed to 240 and 460 mg/kg-day had significantly reduced body weight at weaning in comparison with controls (see Table 4). Although these changes occurred at the end of the period of active nursing and are associated with decreases in maternal water consumption, it is not clear that the reduced weight compared with controls can be attributed only to reduced maternal water intake.

Table 4. Body Weight (g) at Weaning in F_1 and F_2 Rat Pups in a Two-Generation Reproduction Study with Acrylic Acid[a]

	Dose (mg/kg-day)			
Generation	**0**	**53**	**240**	**460**
F_1 Pups (M/F)	52.3/50.1	52.1/49.4	46.6[b]/44.6[b]	34.2[b]/32.7[b]
F_2 Pups (M/F)	50.4/48.4	51.5/48.4	44.6[b]/42.4[b]	34.5[b]/33.2[b]

[a]Hellwig et al. (1997); values are means for males/females; standard deviations are not reported
[b]$p < 0.01$, Dunnett's Test

Slight reductions in the number of pups with eye opening or auditory canal opening on time were statistically ($p < 0.05$) significant in some groups, but were within historical control ranges for rats from this colony (Hellwig et al., 1997) and are not considered to be treatment-related. There were no adverse treatment-related effects on reproductive function at any dose tested. The only clearly treatment-related adverse effects identified by histopathological examination were lesions in the forestomach and glandular stomach in F_0 and F_1 parental animals exposed to 460 mg/kg-day. Minimal hyperkeratosis of the limiting ridge of the forestomach and edema of the submucosa of the glandular stomach were reportedly observed in most animals of

both sexes (data not shown). These lesions were not observed in rats exposed to doses of 53 or 240 mg/kg-day. The NOAEL for reproductive effects is 460 mg/kg-day (highest dose tested). The NOAEL and LOAEL values for parental toxicity are 240 and 460 mg/kg-day, respectively, for histological changes in the stomach and forestomach and reduced body-weight gain in the F_1 parents. The LOAEL for pup toxicity is 240 mg/kg-day on the basis of significant reduction in body weight; the NOAEL for pup toxicity and the overall NOAEL for the study is 53 mg/kg-day.

In a one-generation reproduction study, Fischer 344 rats (10 males, 20 females per group) were administered acrylic acid (≈97% pure) in drinking water at target doses of 0, 83, 250, or 750 mg/kg-day for 13 weeks (DePass et al., 1983). Exposure was continued during a 15-day period of cohabitation (one male, two females) and throughout gestation and lactation. Females were placed into individual cages for nesting. Dates of parturition, litter size, number born live and dead were recorded. Litter size was reduced to five male and five female pups on Day 5 of lactation. Offspring were weighed as litters on Day 7 and individually on Day 21 postpartum. Food and water consumption and body weight were measured daily. Following weaning, 10 rats (5 males, 5 females) from each dose group of F_0 and F_1 were randomly selected for sacrifice and necropsy. Liver, kidney, heart, brain, and testes were weighed, and tissues from these organs from the high-dose and control groups were evaluated microscopically.

No clinical signs or unusual reproductive behaviors were observed (DePass et al., 1983). Table 5 shows the results for body weight, food consumption, water consumption, and organ weights of parental animals. Significant reductions in body-weight gain were observed in parental males at 750 mg/kg-day and females at 250 and 750 mg/kg-day. Food consumption was significantly decreased at 750 mg/kg-day in both sexes, while water consumption was significantly decreased at 250 and 750 mg/kg-day in both sexes. Changes in organ weights appeared to occur in parallel to decreased body-weight gain. No histopathological changes were observed in any of these organs. In the high-dose group, there appeared to be low male and female fertility and decreases from controls in the number of litters with live pups, the number of live pups per litter, and the percent of pups weaned (see Table 6). None of these apparent differences were statistically significant, but interpretation of these results is complicated by unusually low control values for female fertility and number of live pups per litter. It is also unclear how to reconcile the reported decrease in percent of high-dose pups weaned with 100% survival of those pups through Day 21 of weaning. Mean body weight among high-dose pups of both sexes was significantly lower than control values on Postnatal Days 7 and 21 (data for Day 21 are shown in Table 7). Small—but significant—changes in organ weights were noted in parallel with the decreased body weight. As with parental animals, no histological changes were noted in any of these organs. Based on these findings, 250 mg/kg-day is a NOAEL for the study, and 750 mg/kg-day is a LOAEL for reductions in parental and fetal body weight. Possible reproductive effects were also seen at 750 mg/kg-day. Other reported developmental studies (Singh et al., 1972) observed total body-weight reductions pertinent to gestational exposures to acrylic acid monomers. No other developmental effects were observed in this study.

As part of a series of genetic toxicity tests of acrylic acid, a dominant-lethal assay was conducted with male CD-1 mice (McCarthy et al., 1992). Male mice (group sizes were not explicitly reported, but, judging by the numbers of females reported in the results tables, 5–30 males/group were used) received either a single gavage dose of acrylic acid (>99.8% pure, adjusted to pH = 6) in water (0, 32, 108, or 324 mg/kg) or five consecutive daily doses of 0, 16,

Table 5. Body Weight, Food Consumption, Water Consumption, and Organ Weights of Parental Rats Following Exposure to Acrylic Acid in Drinking Water in a One-Generation Reproduction Study[a]

	Dose (mg/kg-day)							
	0		83		250		750	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Males								
Measured dose (g/kg-day)	0.0	0.0	0.085	0.006	0.25	0.02	0.73	0.05
Food consumption (g/rat-day)	16.1	0.2	16.8	0.3	16.2	0.3	14.0[d]	0.07
Water consumption (mL/rat-day)	21.3	0.3	20.1	0.5	17.7[d]	0.5	12.9[d]	1.0
Body-weight gain (g)	206.0	16.9	201.2	25.0	191.7	11.6	143.7[d]	23.0
Liver absolute (g)	12.09	1.67	12.66	0.77	12.05	0.64	9.61[c]	0.57
Liver relative (%)	3.18	0.28	3.46	0.17	3.30	0.16	3.20	0.09
Kidney absolute (g)	2.41	0.24	2.45	0.07	2.36	0.15	2.32[c]	0.39
Kidney relative (%)	0.63	0.03	0.67	0.02	0.64	0.04	0.77[c]	0.09
Spleen absolute (g)	0.63	0.09	0.64	0.05	0.66	0.06	0.66	0.12
Spleen relative (%)	0.17	0.02	0.17	0.01	0.18	0.01	0.22[b]	0.04
Heart absolute (g)	0.96	0.16	0.91	0.08	0.83	0.07	0.78	0.23
Heart relative (%)	0.25	0.03	0.25	0.01	0.23	0.02	0.26	0.06
Brain absolute (g)	1.87	0.19	1.86	0.05	1.89	0.08	1.71	0.26
Brain relative (%)	0.50	0.06	0.51	0.03	0.52	0.03	0.57	0.10
Testes absolute (g)	2.89	0.17	2.88	0.09	2.91	0.06	2.76	0.15
Testes relative (%)	0.77	0.07	0.79	0.06	0.80	0.02	0.92[d]	0.06
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Females								
Measured dose (g/kg-day)	0.0	0.0	0.083	0.003	0.25	0.01	0.72	0.04
Food consumption (g/rat-day)	10.5	0.1	10.7	0.4	0.4	0.4	8.7[d]	0.03
Water consumption (mL/rat-day)	15.1	0.5	14.7	0.3	12.5[d]	0.9	8.8[d]	0.4
Body-weight gain (g)	85.2	8.5	87.4	8.4	78.2[b]	9.4	59.5[d]	8.6
Liver absolute (g)	7.25	0.82	8.51[b]	0.99	8.22	0.72	5.58[c]	0.32
Liver relative (%)	3.43	0.38	3.84[b]	0.22	4.00[c]	0.30	3.32	0.20
Kidney absolute (g)	1.50	0.12	1.69[b]	0.17	1.69[b]	0.09	1.47	0.09
Kidney relative (%)	0.72	0.07	0.77	0.04	0.83[c]	0.04	0.87[d]	0.04
Spleen absolute (g)	0.44	0.05	0.46	0.07	0.45	0.04	0.37[b]	0.03
Spleen relative (%)	0.21	0.03	0.21	0.03	0.22	0.02	0.22	0.02
Heart absolute (g)	0.64	0.10	0.71	0.08	0.68	0.06	0.54	0.09
Heart relative (%)	0.30	0.04	0.32	0.02	0.34	0.04	0.32	0.05
Brain absolute (g)	1.69	0.09	1.74	0.10	1.70	0.13	1.64	0.04
Brain relative (%)	0.80	0.05	0.79	0.03	0.83	0.04	0.98[c]	0.01

[a]DePass et al. (1983)
[b]$p < 0.05$
[c]$p < 0.01$
[d]$p < 0.001$

Table 6. Reproductive Effects in Dams Following Exposure to Acrylic Acid in Drinking Water in a One-Generation Reproduction Study[a]

	Dose (mg/kg-day)			
Endpoint	**0**	**83**	**250**	**750**
Fertility index (males)[b]	80	100	80	60
Fertility index (females)[c]	50	95	75	45
Gestation index[d]	100	100	100	89
Gestation survival index[e]	100	100	100	100
5-Day survival index[f]	100	100	100	100
21-Day survival index[g]	100	100	100	100
Pups born alive/litter[h]	6	8	9	4
Pups weaned/pups alive at birth[h]	100	100	100	42

[a]DePass et al. (1983)
[b]Litters sired per male mated (× 100)
[c]Deliveries per female mated (× 100)
[d]Litters with live pups/total pregnancies (× 100)
[e]Pups born viable/total pups delivered (× 100); median per litter
[f]Pups viable at Day 5/pups born viable (× 100); median per litter
[g]Pups viable at Day 21/pups retained at Day 5 (× 100); median per litter
[h]Median

Table 7. Body Weight, Food Consumption, Water Consumption, and Organ Weights of F_1 Male and Female Rat Pups on Day 21 Postpartum Following Gestational and Lactational Exposure to Acrylic Acid[a]

	Dose (mg/kg-day)							
	0		83		250		750	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Male								
Mean body weight (g)	32.9	6.4	32.2	4.0	32.6	4.2	24.7[c]	4.0
Liver absolute (g)	1.14	0.12	1.32	0.20	1.15	0.14	0.80[c]	0.14
Liver relative (%)	3.55	0.05	3.87	0.27	3.65	0.21	3.06[c]	0.16
Kidney absolute (g)	0.36	0.05	0.39	0.03	0.35	0.04	0.24[c]	0.07
Kidney relative (%)	1.11	0.04	1.14	0.07	1.13	0.06	0.92	0.31
Spleen absolute (g)	0.18	0.02	0.18	0.02	0.18	0.03	0.12	0.02
Spleen relative (%)	0.55	0.10	0.53	0.04	0.58	0.03	0.48	0.06
Heart absolute (g)	0.12	0.03	0.14	0.03	0.12	0.03	0.14	0.12
Heart relative (%)	0.38	0.05	0.40	0.04	0.39	0.04	0.50	0.38
Brain absolute (g)	1.25	0.09	1.25	0.07	1.23	0.14	1.20	0.05
Brain relative (%)	3.89	0.21	3.73	0.48	3.91	0.34	4.63[b]	0.61
Testes absolute (g)	0.15	0.02	0.17	0.03	0.16	0.02	0.13	0.02
Testes relative (%)	0.47	0.02	0.49	0.04	0.51	0.02	0.50	0.03
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Female								
Mean body weight (g)	31.6	5.0	31.8	3.3	31.7	4.1	24.1[c]	4.3
Liver absolute (g)	1.02	0.15	1.34[b]	0.15	1.20	0.17	0.74[b]	0.20
Liver relative (%)	3.53	0.15	3.88	0.17	3.74	0.25	3.16	0.47
Kidney absolute (g)	0.34	0.04	0.40	0.05	0.37	0.04	0.29	0.04
Kidney relative (%)	1.16	0.08	1.15	0.05	1.15	0.08	1.25	0.22
Spleen absolute (g)	0.17	0.04	0.18	0.03	0.16	0.02	0.12	0.03
Spleen relative (%)	0.57	0.12	0.51	0.04	0.49	0.02	0.53	0.08
Heart absolute (g)	0.11	0.02	0.14[b]	0.02	0.12	0.02	0.07[b]	0.02
Heart relative (%)	0.37	0.03	0.42	0.04	0.37	0.04	0.30[b]	0.07
Brain absolute (g)	1.18	0.18	1.24	0.13	1.28	0.04	1.13	0.04
Brain relative (%)	1.03	0.86	3.61	0.30	4.04	0.33	4.98[b]	0.80

[a]DePass et al. (1983)
[b]$p < 0.05$
[c]$p < 0.01$

54, or 162 mg/kg-day, also administered by gavage in water. The doses used in the acute and repeated-dose studies were based on preliminary toxicity studies. The maximum tolerated doses, 324 mg/kg-day for the acute study and 162 mg/kg-day for the repeated-dose study, did not result in mortality ($<LD_1$ determined by probit analysis) or reduction in mating or fertility indices in the preliminary studies. Cyclophosphamide, administered in water by gavage, was used as a positive control (50 mg/kg) in the acute study; 20 mg/kg-day in the repeated-dose study). Each male was placed into a cage with two virgin females immediately following exposure. Females were checked for vaginal plugs each morning, and pregnant females were replaced with virgin females. This process was continued for 46 consecutive days. The uterine contents of pregnant females were examined 12–15 days after the observation of a vaginal plug. The fertility index (number pregnant/number mated), numbers of live and dead implants, number live implants per number of pregnant females and number of dead implants per number of pregnant females were recorded for each 3-day interval up to 46 days. The percentage of dominant-lethals was determined at the same intervals and was defined as 1 - (number of live embryos per exposed pregnant female/number of live embryos per pregnant controls) × 100.

Data are shown only for the maximum dose for the acute and repeated-dose assays (McCarthy et al., 1992). Over multiple intervals in both the acute and repeated-dose assays, cyclophosphamide, the positive control, induced significant increases in the percentage of dead implants and marked increases (statistics were not conducted for dominant-lethal determinations) in the percentage of dominant lethals in comparison with controls. While acrylic acid produced some dominant lethals in some intervals, the percentage of dead implants did not differ significantly from controls in any interval in either the acute or repeated-dose assays. As such, acrylic acid was not considered to have produced dominant-lethal mutations in CD-1 mice. The NOAEL values for reproduction in the acute and repeated-dose studies are 324 mg/kg and 162 mg/kg-day, respectively.

Inhalation Exposure

Subchronic Studies—Based on results obtained from a 2-week probe study (Miller et al., 1981), Fischer 344 rats and $B6C3F_1$ mice (15/sex/species) were exposed by whole-body inhalation to acrylic acid vapors (99.7% pure) at measured concentrations of 0, 5, 25, or 75 ppm (0, 14.9, 74.7, or 224 mg/m^3) for 6 hours/day, 5 days/week, for 13 weeks (Miller et al., 1981). Body weight was determined on the first day of exposure, then intermittently throughout the remainder of the study and immediately before sacrifice. Animals were observed twice a day for clinical signs of toxicity. Hematology (RBC, Hgb, Hct, total and differential WBC) and serum chemistry (glucose, BUN, ALP, ALT) were evaluated in 10 rats and 10 mice of each sex and exposure group, and urinalysis (specific gravity, pH, glucose, protein, ketones, bilirubin, urobilinogen, and blood) was conducted on 10 rats of each sex per group. Gross necropsy was performed on all animals that died or were sacrificed at the end of the study, and weights of the brain, heart, liver, kidneys, and testes were recorded. Histological examination was conducted for 10 animals of each sex and species in the control and 75-ppm (224-mg/m^3) groups. Organs identified as targets in the high-dose groups were also evaluated in the mid- and low-dose groups.

Mortality occurred in two mice: one female in the high-dose group and one male in the mid-dose group (Miller et al., 1981). Deaths were not considered to be treatment-related and were attributed to trauma during handling by the researchers. An additional high-dose female

mouse was sacrificed in moribund condition after 5–6 weeks of exposure. No rats died during the study. Female mice in the mid- and high-dose groups had significantly ($p < 0.05$) reduced body-weight gain when compared to controls after 12 weeks of exposure—but not before (see Table 8). There were no significant treatment-related effects on body-weight gain for male mice or for rats of either sex. The authors reported that there were no significant treatment-related effects on organ weights, organ-to-body weight ratios, hematology, or clinical chemistry in rats or mice, or urinalysis in rats (data not shown). Male mice in the mid- and high-dose groups and females in the high-dose group had lower mean hemoglobin levels than controls, but these levels were considered to be in the normal range for mice of similar age and strain. The researchers reported no gross pathological observations in rats or mice related to treatment. Lesions of the nasal mucosa were observed during histopathological examination of rats and mice, primarily degeneration of the olfactory epithelium (Table 9). The incidence and severity of these lesions increased with exposure concentration. There were no other significant treatment-related histopathological findings. For rats, the NOAEL and LOAEL values for the study are 25 ppm (74.7 mg/m^3) and 75 ppm (224 mg/m^3) based on slight focal degeneration of the olfactory epithelium. For mice, the low exposure level of 5 ppm (14.9 mg/m^3) is a LOAEL for focal degeneration of the nasal olfactory epithelium.

Table 8. Body-Weight Gains (Mean ± SD) of Rats and Mice in a 13-Week Vapor Inhalation Study of Acrylic Acid[a]

Weeks on Test	Exposure Concentration (mg/m^3)							
	Control	14.9	74.7	224	Control	14.9	74.7	224
	Male Rats				Female Rats			
3	91 ± 10	89 ± 8	91 ± 9	84 ± 11	38 ± 4	40 ± 4	41 ± 3	40 ± 4
6	157 ± 11	156 ± 9	156 ± 10	148 ± 13	67 ± 6	69 ± 5	68 ± 4	65 ± 5
9	195 ± 14	192 ± 10	195 ± 11	188 ± 15	81 ± 6	84 ± 4	83 ± 4	80 ± 6
12	213 ± 15	210 ± 14	219 ± 13	210 ± 14	86 ± 7	89 ± 4	89 ± 7	87 ± 7
	Male Mice				Female Mice			
3	3.5 ± 1.7	4.0 ± 0.7	3.7 ± 0.6	4.5 ± 0.8[b]	5.0 ± 1.1	5.5 ± 1.7	4.6 ± 0.9	4.7 ± 1.0
6	4.5 ± 0.8	6.6 ± 1.7[b]	5.8 ± 1.6	6.1 ± 1.0[b]	6.9 ± 1.1	7.7 ± 1.0	6.2 ± 0.7	6.8 ± 0.9
9	6.3 ± 2.0	8.3 ± 2.6[b]	6.9 ± 1.5	7.6 ± 1.4	8.4 ± 1.0	10.1 ± 2.7[b]	7.6 ± 1.0	8.4 ± 1.3
12	7.4 ± 2.0	9.3 ± 2.5[b]	7.5 ± 2.0	8.5 ± 1.5	9.8 ± 1.3	8.9 ± 1.2	8.6 ± 1.1[b]	8.7 ± 1.1[b]

[a]Miller et al. (1981)
[b]Statistically significant deviation from control group mean using Dunnett's Test $p < 0.05$

Table 9. Histopathological Observations in the Nasal Mucosa of Rats and Mice After Exposure to Acrylic Acid in a 13-Week Vapor Inhalation Study[a,b]

	Exposure Concentration (mg/m^3) Sex/Species							
	0	**14.9**	**74.7**	**224**	**0**	**14.9**	**74.7**	**224**
Lesion Type	**Male Rats**				**Female Rats**			
Slight focal degeneration of the olfactory epithelium	0/10	0/10	0/10	7/10	0/10	0/10	0/10	10/10
	Male Mice				**Female Mice**			
Focal degeneration of the olfactory epithelium in the dorso-medial aspect of the nasal passages with partial replacement by an epithelium resembling respiratory epithelium –slight-to-moderate	1/10	1/10	0/11	10/10	0/10	0/10	0/10	10/12
Focal degeneration of olfactory epithelium in the dorso-medial aspect of the nasal passages								
–slight	0/10	0/10	10/11	0/10	0/10	0/10	9/10	1/12
–very slight	1/10	1/10	1/11	0/10	0/10	4/10	0/10	0/12
–ungraded due to autolysis	0/10	0/10	0/11	0/10	0/10	0/10	0/10	1/12
Focal infiltration of inflammatory cells in the mucosa and submucosa in regions having degeneration of the mucosa								
–slight	0/10	0/10	0/11	0/10	0/10	0/10	2/10	0/12
–very slight	0/10	0/10	1/11	10/10	0/10	0/10	0/10	10/12
Focal hyperplasia of submucosal glands in regions having degeneration of the mucosa –very slight	0/10	0/10	0/11	10/10	0/10	0/10	0/10	10/12

[a] Miller et al. (1981)
[b] Histopathological examinations were performed for 10 rats and 10 mice of each exposure group as well as for any animals that died or were sacrificed moribund prior to scheduled sacrifice

Reproductive/Developmental Studies—In a preliminary developmental toxicity study, pregnant Sprague-Dawley rats (5 females/group) were exposed by whole-body inhalation to acrylic acid vapor (99.74% pure) at mean measured concentrations of 0, 217.6 or 438.9 ppm (0, 641, or 1290 mg/m^3 for 6 hours/day, for 10 consecutive days on Gestation Days (GD) 6–15 (Klimisch and Hellwig, 1991). This study was conducted in order to determine appropriate concentrations of test substance to be used in the main study summarized below. Body weight and food consumption were determined prior to the test, then every 3 days during the testing period until Day 20. All rats were sacrificed on Day 20 and received gross pathological examination that included determination of uterine weight, number of implantation sites, and the number of live and dead fetuses. A histological examination of the nasal mucosa was conducted for all adults. Weight and crown-rump length were recorded for each fetus as well as any external malformations.

No dams died during the study (Klimisch and Hellwig, 1991). Body weight and food consumption were decreased throughout the entire exposure period in high-dose rats. At the low dose, body-weight gain and food consumption were decreased only during the first 3 days of exposure. All treated animals showed clinical signs of toxicity. In the low-dose group, signs

included eyelid closure, eye discharge, and slightly red noses. Clinical signs were more pronounced in the high-dose group, with increased restlessness and more frequent snout rubbing. Body weight minus uterus weight, body-weight gain minus uterus weight, and placental weight were significantly ($p < 0.05$) decreased in high-dose rats in comparison with controls. Terminal placental weights were also significantly decreased in the low-dose group. Slight degeneration of the nasal olfactory epithelium with metaplasia of the respiratory epithelium and hyperplasia of the submucosal gland was observed during histopathological examination in both dose groups (data not shown). Due to the limited number of pregnancies and fetuses present, embryonic and fetal toxicity assessments were not conducted. Based on these findings, the study authors concluded that maternal toxicity was present at both concentrations tested and identified the low concentration of 217.6 ppm (641 mg/m^3) as a LOAEL for clinical signs of toxicity, reduced placental weight, and degeneration of the nasal olfactory epithelium.

In the full developmental toxicity study, pregnant Sprague-Dawley rats (30 females/group) were exposed to acrylic acid vapor at mean measured concentrations of 0, 39.4, 114.0, or 356.2 ppm (0, 116, 336, or 1050 mg/m^3) for 6 hours/day, 5 days/week on GD 6–15 (Klimisch and Hellwig, 1991). As in the pretest, body weight and food consumption were determined prior to the test, and then every 2 days during the testing period until Day 20. All rats were sacrificed on Day 20 and received gross pathological examination that included weight of the uterus, number of implantation sites, and number of live and dead fetuses. Fetuses were weighed and measured. One-third of the fetuses were stained and examined for internal malformations. The remaining two-thirds were examined for skeletal malformations.

No maternal deaths were observed during the study (Klimisch and Hellwig, 1991). Animals in the high-dose group had a watery discharge from the eyes and nose, and had restless behavior that continued for 1–2 hours after exposure. As shown in Table 10, there were small—but significant—reductions in maternal body weight and body-weight gain in comparison to controls, primarily in the high-dose group, but, also, to a lesser extent in the mid- and low-dose groups. Food consumption was reduced in a dose-related manner and was statistically significant during the first few days of exposure in the mid-dose group and throughout the duration of the study in the high-dose group. The data showed no treatment-related effects on the number of *corpora lutea*, implantations, or live and dead fetuses. No fetal mortality was observed during the study. Mean fetal body weights were significantly higher than control values in the mid- and high-dose groups, but this change was not considered to be toxicologically relevant. Fetal length was not affected by treatment. The data showed no treatment-related external, internal, or skeletal anomalies. Based on these findings, the NOAEL and LOAEL values for maternal toxicity are 39.4 ppm (116 mg/m^3) and 114 ppm (336 mg/m^3), respectively, based on reduced body weight. The NOAEL for developmental toxicity is the highest dose tested: 356.2 ppm (1050 mg/m^3).

Table 10. Effects on Body and Uterine Weight (Mean ± SD) in Pregnant Female Rats Exposed to Acrylic Acid Vapors[a]

Endpoint	Exposure Concentration (mg/m^3)			
	0	116	336	1050
Body weight (Day 0)	216 (9.4)[b]	216 (11.3)	214 (7.7)	215 (9.9)
Body weight (Day 6)	243 (10.1)	243 (16.1)	242 (9.5)	242 (12.7)
Body weight (Day 15)	288 (9.6)	284 (19.2)	283 (14.4)	261 (16.3)[f] -9%[g]
Body weight (Day 20)	354 (19.9)	349 (33.3)	346 (27.0)	333 (26.1)[f] -5.9%[g]
Uterus weight (Day 20)	64 (18.8)	66 (25.5)	68 (23.6)	65 (21.1)
BWE-uterus[c]	290 (12.0)	283 (17.8)	278 (16.6)[f] -4.1%[g]	267 (13.4)[f] -7.9%[g]
BWE-BWS-uterus[d]	74 (11.5)	67 (11.2)[e] -9.5%[g]	65 (13.1)[f] -12.2% [g]	52 (9.5)[f] -29.7% [g]

[a]Klimisch and Hellwig (1991)
[b]Figures in parenthesis indicate standard deviations
[c]BWE-uterus = body weight on Day 20 minus uterus weight
[d]BWE-BWS-uterus = body-weight gain between Day 0 and Day 20 minus uterus weight
[e]$p < 0.05$
[f]$p < 0.01$
[g]Percent difference from controls

As part of a larger study designed to address the embryotoxicity of acrylates, pregnant Sprague-Dawley rats (20–24 per group) were exposed by whole-body inhalation to 0, 50, 100, 200, or 300-ppm acrylic acid (>99% pure) (0, 147, 295, 589, or 884 mg/m^3) for 6 hours/day on GD 6–20 (Saillenfait et al., 1999). Measured exposure concentrations were within 5% of target concentrations, as confirmed by laboratory analysis of the test atmospheres. Body weight and food consumption were measured periodically. Dams were euthanized on GD 21, and number of implantation sites, resorptions, and dead and live fetuses were recorded. Live fetuses were weighed, sexed, and examined for external anomalies. Half of the fetuses were examined for internal tissue malformations; the other half were stained and examined for skeletal anomalies.

There was no mortality (Saillenfait et al., 1999). Maternal body-weight gain during gestation (GD 6–21) was significantly ($p < 0.05$) reduced in comparison with control values among dams exposed to 200- or 300-ppm acrylic acid (Table 11). Food consumption during gestation (GD 6–21) was significantly reduced in the 100-, 200-, and 300-ppm groups (Table 11). The data showed no toxicologically relevant effects on the mean number of implantation sites, number of resorptions, number of live fetuses or sex of fetuses. There was a concentration-related decrease in mean fetal body weight per litter that was statistically significant at 300 ppm for males, females, and both sexes combined (Table 12). The data showed no toxicologically relevant effects on the number of external, internal, or skeletal malformations. The NOAEL for maternal toxicity in this study is 100 ppm (295 mg/m^3). The LOAEL for maternal toxicity is 200 ppm (589 mg/m^3) based on decreased body-weight gain during GD 6–21. The NOAEL and LOAEL for fetal toxicity are 200-ppm (589 mg/m^3) and 300-ppm (884 mg/m^3), respectively, for decreased fetal body weight.

Table 11. Effects of Exposure to Acrylic Acid Vapors on Pregnant Sprague-Dawley Rats[a]

Acrylic Acid Concentration (ppm/6 hr/day)	No. of Dams	Body Weight (g) on GD 6	Body Weight Gain (g) on GD			Absolute Weight Gain (g)[b]
			6-13	13-21	6-21	
0	24	272 ± 16	30 ± 7	102 ± 29	131 ± 32	27 ± 13
50	20	265 ± 15	25 ± 11	108 ± 25	132 ± 25	29 ± 9
100	22	269 ± 12	25 ± 8	101 ± 18	126 ± 22	21 ± 12
200	21	269 ± 14	18 ± 6[c]	87 ± 19	105 ± 21[c]	5 ± 12[c]
300	23	268 ± 16	12 ± 8[c]	75 ± 15[c]	88 ± 18[c]	-13 ± 14[c]
			Food Consumption (g/dam/day) on GD			
			0-6	6-13	13-21	6-21
0	24		22 ± 2	23 ± 2	26 ± 3	25 ± 3
50	20		23 ± 2	21 ± 2[d]	26 ± 2	24 ± 2
100	22		23 ± 2	21 ± 2[d]	25 ± 2	23 ± 1[d]
200	21		23 ± 2	19 ± 1[c]	23 ± 2[c]	21 ± 1[c]
300	23		23 ± 2	18 ± 2[c]	20 ± 2[c]	19 ± 2[c]

[a]Saillenfait et al. (1999); values are mean ± SD
[b](Day 21 body weight)—(gravid uterus weight)—(Day 6 body weight)
[c]Significant difference from control value, $p < 0.01$, Dunnett's Test
[d]Significant difference from control value, $p < 0.05$, Dunnett's Test

Table 12. Effects of Gestational Exposure to Acrylic Acid Vapors on Sprague-Dawley Rats[a]

Concentration (ppm/6 hr/day)	No. Litters	Mean Fetal Body Weight (g) per Litter		
		All	Males	Females
0	24	5.73 ± 0.20	5.89 ± 0.25	5.58 ± 0.18
50	20	5.72 ± 0.39	5.89 ± 0.34	5.52 ± 0.39
100	22	5.60 ± 0.31	5.75 ± 0.29	5.47 ± 0.32
200	21	5.38 ± 0.32	5.73 ± 0.35	5.42 ± 0.34
300	23	5.22 ± 0.37[b]	5.36 ± 0.40[b]	5.09 ± 0.34[b]

[a]Saillenfait et al. (1999); values are mean ± SD
[b]Significant difference from control value, $p < 0.01$, Dunnett's Test

In a range-finding study in rabbits, groups of eight pregnant New Zealand white rabbits were exposed to 0-, 30-, 60-, 125-, or 250-ppm acrylic acid (>99% pure) on GD 10–23 (Neeper-Bradley et al., 1997). Test concentrations were analytically verified. From each group, three animals were necropsied on GD 23 (last day of exposure), and the remaining animals were examined on GD 29. Clinical signs of nasal irritation were significantly increased in the 250-ppm group and observed to a lesser extent in the 125-ppm group. Body weight on GD 29 was reduced in a dose-related fashion in all treated groups; the difference from controls was statistically significant in all groups except those exposed to 60 ppm. Histopathological

examination of the does revealed lesions in the nasal turbinates in all treated groups, ranging from rhinitis to squamous metaplasia, epithelial erosion, and ulceration of the epithelium; severity of the nasal lesions increased with increasing exposure concentration.

In the full developmental study (Neeper-Bradley et al., 1997), groups of 16 pregnant rabbits were exposed to 0-, 25-, 75-, or 225-ppm acrylic acid (>99% pure) (0, 73.7, 221, or 663 mg/m^3) 6 hours per day on GD 6–18. Test concentrations were analytically verified. Signs of nasal irritation (perinasal encrustacean, perinasal wetness, and nasal congestion) were significantly increased in the high-dose group (225 ppm). Nasal congestion was also observed in one mid-dose animal. The maternal body weight data showed no effect of treatment at any exposure level. Histological examination of maternal tissues was not performed. The data showed no exposure-related adverse effects on the number of *corpora lutea* and total, viable, or nonviable implantations; preimplantation loss; fetal length or weight; or on morphological abnormalities (external, skeletal, or soft tissue). The NOAEL for maternal toxicity in this study is 75 ppm (221 mg/m^3). The LOAEL for maternal toxicity is 225 ppm (663 mg/m^3) based on nasal irritation. The high exposure level of 225 ppm (663 mg/m^3) is a NOAEL for developmental toxicity in this study.

OTHER STUDIES

Toxicokinetics

Toxicokinetic studies of acrylic acid with mice and rats demonstrate that (1) acrylic acid is rapidly absorbed, metabolized, and excreted in a similar manner, regardless of the route of exposure; and (2) the disposition of acrylic acid is qualitatively and quantitatively similar in mice and rats.

Sprague-Dawley rats were exposed to acrylic acid either by nose-only inhalation (^{11}C-acrylic acid at a maximum dose of 26 mg/kg for one minute) or by gastric intubation (aqueous solution of ^{11}C-acrylic acid; dose equivalent to that used in inhalation experiment) (Kutzman et al., 1982). Rats in the inhalation study were euthanized 1.5 or 65 minutes after exposure. Rats in the oral study were killed at 1.5, 10, 20, 40, or 65 minutes after exposure. An examination of the radioactivity in organs at the various time points indicated that regardless of the route of exposure, the gastrointestinal tract was the primary site of absorption and the percentage of radioactivity expired by the lungs (approximately 60%) and in the urine (approximately 6%) was similar.

The absorption, distribution, metabolism, and elimination of acrylic acid were studied following oral (40 or 150 mg/kg) or dermal administration (10 or 40 mg/kg) of ^{14}C-acrylic acid to male C3H mice and F344 rats (Black et al., 1995). In all cases, acrylic acid was rapidly absorbed, metabolized, and eliminated. In the oral studies with both species, approximately 80% of the administered dose was exhaled as $^{14}CO_2$, 3% was eliminated in the urine, and 1% was eliminated in the feces. In the dermal studies with both species, 12–26% of the applied dose was absorbed; the rest was presumed to be evaporated. For both species, 80% of the absorbed radioactivity was exhaled within 24 hours; less than 0.5% of the administered dose was excreted in the urine and feces. In both species and following both oral and dermal exposure, acrylic acid was rapidly distributed to the plasma, liver, kidneys, and fat; elimination from these compartments was rapid, but was slower from the fat.

Other Routes

No increase in skin tumors developed in a group of 40 male C3H/HeJ mice that received applications to the skin of 25 mL of 1% acrylic acid (~0.2 mg acrylic acid per mouse or 6.7 mg/kg) 3 times weekly for life compared to acetone controls (DePass et al., 1984). A similar study observed no increase in skin tumors in male or female C3H or ICR mice treated with doses up to 100 mL of 1% acrylic acid (~1.0 mg per mouse or 37.9 mg/kg) in acetone 3 times weekly for 21 months (Hoechst-Celanese, 1990). There was a statistically significant increase in the incidence of lymphosarcoma in female C3H mice in the high-dose group (7/50 vs. 0/50 in acetone controls) of this study, but it is unclear if this resulted from treatment.

Genotoxicity

Acrylic acid was negative in mutagenicity tests in *S. typhimurium* (strains TA100, TA1535, TA1537, TA1538, and TA98) with or without metabolic activation (Zeiger et al., 1987; Lijinsky and Andrews, 1980). A test for mutagenicity of acrylic acid at the tk locus in L5178Y mouse lymphoma cells without exogenous activation was positive, but, because it was primarily small-colony mutants that were induced, the researchers suggested the positive results were due to a clastogenic mechanism rather than induction of point mutations (Moore et al., 1988). Acrylic acid gave positive results for induction of chromosomal aberrations in mouse lymphoma cells in this study (Moore et al., 1988). McCarthy et al. (1992) reported negative results for acrylic acid in a test for mutagenic activity at the HGPRT locus in Chinese hamster ovary (CHO) cells but positive results for chromosomal aberrations in CHO cells—with or without activation. However, acrylic acid did not induce micronucleus formation in Syrian hamster embryo (SHE) cells (Wiegand et al., 1989), and results were negative in assays for both mutagenicity and clastogenicity in vivo (*Drosophila* sex-linked recessive lethal, dominant lethal in mice, chromosomal aberrations in mouse bone marrow cells) (McCarthy et al., 1992). Assays for DNA damage (unscheduled DNA synthesis) in cultured rat hepatocytes and SHE cells were negative (McCarthy et al., 1992; Wiegand et al., 1989), as was an assay for morphological transformation in SHE cells (Wiegand et al., 1989).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RFD VALUES FOR ACRYLIC ACID

SUBCHRONIC p-RfD

Table 13 summarizes the available oral toxicity database for acrylic acid. For the 90-day gavage study (Hellwig et al., 1993) in Wistar rats, the endpoint incidences were summarized but no statistical analysis were reported and no conclusions regarding organ weights were reported. There was no discussion on timing of mortality and clinical signs reported associated with animals that died. This effect could possibly be related to bolus dosing. The reported frank effect level (FEL) of 107 mg/kg-day based on mortality does not give support for use as POD for deriving RfD value.

The 12-month drinking water study (Hellwig et al., 1993) in Wistar rats for both sexes, contained a satellite group that was sacrificed after 90-day exposure. Results of tests performed (feed consumption, drinking water and body weight, hematological, clinical chemistry, pathological and histological examination) showed statistical significance in some cases. The

Table 13. Summary of Oral Noncancer Dose-Response Information for Acrylic Acid

Species and Study Type (*n*/Sex/Group)	Exposure (Doses, Route, Frequency, Duration)	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Duration-Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Subchronic Studies							
F344 rat (15/sex/group)	0, 83, 250, 750mg/kg-d, drinking water, 90 days	83	250	250	Reduced body-weight gain in females		DePass et al., 1983
Wistar rat (10/sex/group)	0, 150, 375 mg/kg-d, gavage (water), 5d/wk, 90 days	None	150 (FEL)	107 (FEL)	Mortality was observed in five males and five females; 15/20 died at the high dose	Forestomach and stomach irritation; necrotizing tubular nephrosis was observed in all animals that died	Hellwig et al., 1993
Wistar rat (20/sex/main group; 10/sex/satellite group)	0, 120, 800, 2000, 5000 ppm (0, 9, 61, 140, 331 mg/kg-d), drinking water, 3 months (satellite group) or 12 months (main group)	331	None	None	None		Hellwig et al., 1993
Chronic Studies							
Wistar rat (50/sex/group)	0, 120, 400, 1200 ppm (0, 8, 27, 78 mg/kg-d), drinking water, 26 months (male), 28 months (female)	78	None	None	None	No effect on tumor incidence, but the maximum tolerated dose apparently was not achieved	Hellwig et al., 1993
Developmental/Reproductive Toxicity Studies							
Wistar rat, two-generation reproduction study (25/sex/group)	0, 500, 2500, 5000 ppm (0, 53, 240, 460 mg/kg-d), drinking water, 70–98 days premating, during mating, gestation, and lactation	Parental: 240 Pups: 53	Parental: 460 Pups: 240	Parental: 460 Pups: 240	Parental: Lesions in stomach and forestomach; body-weight reduction in F_1 parents Pups: Reduction in pup body weight	The NOAEL for reproduction was 460 mg/kg-day	Hellwig et al., 1997
F344 rat, one-generation reproduction study (10 M, 20 F/group)	0, 83, 250, 750 mg/kg-d, drinking water, 13 wks premating, during mating, and throughout gestation and lactation	Parental and pup: 250	Parental and pup: 750	Parental and pup: 750	Parental: Reduced body-weight gain Pup: Reduced body weight		DePass et al., 1983

Table 13. Summary of Oral Noncancer Dose-Response Information for Acrylic Acid

Species and Study Type (*n*/Sex/Group)	Exposure (Doses, Route, Frequency, Duration)	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Duration-Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
CD-1 mouse, dominant-lethal assay (5–30 M/9–59 F/group)	0, 16, 54, 162, gavage, five consecutive daily doses; or 0, 32, 108, 324 mg/kg, gavage, one dose	5 doses: 162 1 dose: 324	None	None	None	No effects on % dead implants or % dominant lethal	McCarthy et al., 1992

[a]Adjusted to continuous exposure

difference between groups in the clinico-chemical, hematological and urinalyical examination at various intervals showed non-obvious treatment related patterns in parameters monitored. The differences were marginal, inconsistent or lacked a dose-effect relationship. The small change in body weight observed in high-dose males was not considered biologically significant. A NOAEL of 331 mg/kg-day (highest dose tested) was identified (six times higher than the NOAEL identified at Hellwig et al. (1997) study.

The 26/28-month drinking water carcinogenicity study (Hellwig et al., 1983) did not reveal any clear toxic or oncogenic effects of acrylic acid with exception of slightly reduce consumption of water, which was not statistically significant. Based on these findings, the NOAEL for this study is 78 mg/kg-day (highest dose tested). Overall, no treatment-related mortality was observed in 90–day, 12-month, or 2-year studies in which Wistar and F344 rats were exposed to acrylic acid via drinking water. This study gives no relevant information for toxicity values assessment in comparison to Hellwig et al. (1997).

The McCarthy et al. (1992) identified a NOAEL value for reproduction in the acute and repeated-dose studies of 324 mg/kg-days and 162 mg/kg-day respectively. This study was not suitable for POD and is less relevant for humans compared to other studies (Hellwig et al., 1993; Hellwig et al., 1997).

The study by Hellwig et al. (1997) (principal study) had an adequate number of animals (25/Sex/rats). It was well described with a clear dosing regimen, sampling strategy and culling of animals. The study was well performed, with four dosing levels including a control group, a range of tissues examined endpoints and exposure levels. Treatment-related differences between controls and animals exposed to acrylic acid observed were statistically significant. The identified NOAEL for pup toxicity was 53 mg/kg-day, lowest compared to other NOAELs identified in other studies (DePass et al., 1983; Hellwig et al., 1993; McCarthy et al., 1992).

The NOAEL of 53 mg/kg-day is the appropriate point of departure (POD) for deriving the subchronic p-RfD for acrylic acid. Other studies (DePass et al., 1983) reported a NOAEL (83 mg/kg-day) and a LOAEL (250 mg/kg-day) that are comparable to the selected POD. Benchmark dose modeling cannot be conducted for reduced pup body weight in the critical study due to the absence of standard deviations or standard errors in the study report.

Using the NOAEL of 53 mg/kg-day from the two-generation reproduction study in Wistar rats (Hellwig et al., 1997) as the POD, a subchronic p-RfD is derived for acrylic acid as follows:

$$\begin{aligned} \textbf{Subchronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 53 \text{ mg/kg-day} \div 300 \\ &= \mathbf{0.2 \text{ or } 2 \times 10^{-1} \text{ mg/kg-day}} \end{aligned}$$

The composite uncertainty factor (UF) of 100 is composed of the following UFs:

- UF_A: A factor of 10 is applied for animal-to-human extrapolation, as data for evaluating relative interspecies sensitivity are insufficient.
- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, as data for evaluating susceptible human response are insufficient.

- UF_D: A factor of 3 is applied due to the absence of a developmental toxicity study by oral exposure.
- UF_L: A factor of 1 is applied because the POD was developed using a NOAEL.
- UF_S: A factor of 1 is applied because further adjustments for duration of exposure are not warranted when developmental toxicity data are used to develop a POD (U.S. EPA, 1991).

Confidence in the principal study is high because a sufficient number of animals were used, appropriate endpoints were measured, and reporting was generally adequate. It is noted, however, that BMD modeling could not be performed because no measure of variation was reported for the critical endpoint of pup body weight. Confidence in the database is high. The database contains three subchronic studies in two strains of rat, a chronic rat study, one- and two-generation reproduction studies in rats, and a dominant lethal assay in mice by oral exposure. The database also includes developmental toxicity studies in rats and rabbits by inhalation exposure. All of these studies are of good quality and present consistent findings. High confidence in the subchronic p-RfD follows.

CHRONIC p-RfD

A chronic RfD of 0.5 mg/kg-day for acrylic acid is available on IRIS (U.S. EPA, 2009a), and it is based on the two-generation reproduction study in rats (Hellwig et al., 1997). As for the subchronic p-RfD presented above, the chronic RfD was calculated from the NOAEL of 53 mg/kg-day for reduced pup weight and a composite UF of 100 (10 each for extrapolation from rats to humans and protection of sensitive individuals). This assessment was posted to IRIS on 2/17/1994.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RFC VALUES FOR ACRYLIC ACID

SUBCHRONIC p-RfC

Table 14 summarizes the available inhalation toxicity database for acrylic acid. Nasal irritation and decreased body weight are the only critical effects that have been observed in rats, mice, and rabbits following subchronic and gestational exposure to acrylic acid by the inhalation route. Degeneration of the nasal olfactory epithelium observed histopathologically is the most sensitive endpoint, with the lowest database LOAEL of 14.9 mg/m^3 ($LOAEL_{[HEC]}$ = 0.33 mg/m^3) observed in a subchronic inhalation study conducted with $B6C3F_1$ mice (Miller et al., 1981). A subchronic LOAEL (3.9 mg/m^3, Miller et al., 1981) in rats and maternal (84mg/m^3) fetal LOAEL (221 mg/m^3) reported in Klimish and Hellwig (1991) and Saillenfait et al. (1999) were comparable to the selected POD. The data sets for focal degeneration of the nasal olfactory epithelium in male and female mice (Table 15) were amenable to benchmark dose modeling. Details of benchmark dose modeling for the data sets shown in Table 15 are given in Appendix A. The data set for female mice yielded a lower benchmark concentration (BMC_{10}) and associated 95% lower confidence limit ($BMCL_{10}$) values of 5.58 and 0.76 mg/m^3, respectively compared to male data. The logprobit model was selected on the basis of the lowest $BMCL_{10}$ from the range of 0.76 to 6.09 mg/m^3.

Table 14. Summary of Inhalation Noncancer Dose-Response Information for Acrylic Acid[a]

Species and Study Type (*n*/Sex/Group)	Exposure (Concentrations, Frequency, Duration)	NOAEL (mg/m^3)	LOAEL (mg/m^3)	$NOAEL_{[HEC]}$ (mg/m^3)	$LOAEL_{[HEC]}$ (mg/m^3)	Responses at the LOAEL	Comments	Reference
Subchronic Toxicity								
F344 rat (15/sex/group)	0, 5, 25, 75 ppm (0, 14.9, 74.7, 224 mg/m^3), 6 h/d, 5 d/wk, 13 wks	74.7	224	1.3	3.9	Slight focal degeneration of the nasal olfactory epithelium		Miller et al., 1981
$B6C3F_1$ mouse (15/sex/group)	0, 5, 25, 75 ppm (0, 14.9, 74.7, 224 mg/m^3), 6 h/d, 5 d/wk, 13 wks	None	14.9	None	0.33	Decreased mean body-weight gain and focal degeneration of the nasal olfactory epithelium		Miller et al., 1981
Reproductive/Developmental Toxicity								
SD rat (30 F/ group)	0, 39.4, 114.0, 356.2 ppm (0, 116, 336, 1050 mg/m^3), 6 h/d, GDs 6–15	Maternal: 116 Fetal: 1050	Maternal: 336 Fetal: None	Maternal: 29 Fetal: 262	Maternal: 84 Fetal: None	Maternal: Reduced body-weight gain on GDs 15–20.	No effects were observed on indices of fertility or fetal development	Klimisch and Hellwig, 1991
SD rat (20–24 F/ group)	0, 50, 100, 200, 300 (0, 147, 295, 589, 884 mg/m^3), 6 h/d, GDs 6–20	Maternal: 295 Fetal: 589	Maternal: 589 Fetal: 884	Maternal: 74 Fetal: 147	Maternal: 147 Fetal: 221	Maternal: Decreased body-weight gain on GDs 6–21: Fetal: Decreased body weight		Saillenfait et al., 1999
New Zealand rabbit (16 F/ group)	0, 25, 75, 225 ppm (0, 73.7, 221, 663 mg/m^3), 6 h/d, GDs 6–18	Maternal: 221 Fetal: 663	Maternal: 663 Fetal: None	Maternal: 31 Fetal: 166	Maternal: 94 Fetal: None	Maternal: Nasal congestion and irritation	No effects on fetal development were observed	Neeper-Bradley et al., 1997

[a]HEC calculated as follows: $NOAEL_{[HEC]}$ = NOAEL × exposure hours/24 hours × exposure days/7 days × dosimetric adjustment

For systemic effects, the dosimetric adjustment is the ratio of the animal:human blood:gas partition coefficients for acrylic acid (in the absence of experimental values, a default value of 1 was used)

For respiratory effects, the dosimetric adjustment is the RGDR for the affected portion of the respiratory tract (extrathoracic for acrylic acid), calculated as the ratio of the animal:human minute volume/surface area ratios using default values from EPA (1994b)

Table 15. BMD Dataset for Incidence of Focal Degeneration of the Nasal Olfactory Epithelium in Mice[a]

	Exposure Concentrations (mg/m^3)			
Sex	**0**	**14.9**	**74.7**	**224**
Male	1/10	2/10	11/11	10/10
Female	0/10	4/10	9/10	11/11

[a]Miller et al. (1981); incidences are based on very slight to moderate focal degeneration of the nasal olfactory epithelium of the dorso-medial aspect of the nasal passages with or without partial replacement with respiratory epithelium

The $BMCL_{10}$ of 0.76 mg/m^3 for the increased incidence of focal degeneration of the nasal olfactory epithelium in female mice is the appropriate POD for deriving a subchronic p-RfC for acrylic acid. Given that the effect of interest associated with the POD is an extrathoracic respiratory effect, acrylic acid was treated as a Category 1 gas, and the following dosimetric adjustments were made to convert the rodent $BMCL_{10}$ to a human equivalent concentration (HEC) (U.S. EPA, 1994b). First, the duration-adjusted $BMCL_{10}$ was calculated:

$$\begin{aligned} BMCL_{10[ADJ]} &= BMCL_{10} \times \text{hours/day} \times \text{days/week} \\ &= 0.76 \text{ mg/m}^3 \times 6/24 \text{ hrs/day} \times 5/7 \text{ days/week} \\ &= 0.14 \text{ mg/m}^3 \end{aligned}$$

Next, the Regional Gas Deposition Ratio (RGDR) for the extrathoracic region was calculated, as follows (Equation 4–18 and default values from U.S. EPA, 1994b):

$$RGDR_{ET} = \frac{(V_E \div SA_{ET})_{mouse}}{(V_E \div SA_{ET})_{human}} = 0.137$$

Where:

V_E = Minute volume (L/min)
= 0.028 L/min for female B6C3F$_1$ mice and 13.8 L/min for humans

SA_{ET} = Surface area of the extrathoracic region (cm^2)
= 3 cm^2 for mice, 200 cm^2 for humans

The $BMCL_{10[HEC]}$ of 0.02 mg/m^3 was subsequently derived as

$$\begin{aligned} BMCL_{10[HEC]} &= RGDR_{ET} \times BMCL_{10[ADJ]} \\ &= 0.137 \times 0.14 \text{ mg/m}^3 \\ &= 0.02 \text{ mg/m}^3 \end{aligned}$$

To derive the subchronic p-RfC for acrylic acid, a composite UF of 30 was applied to the $BMCL_{10[HEC]}$, as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= BMCL10_{[HEC]} \div UF \\ &= 0.02 \text{ mg/m}^3 \div 100 \\ &= \textbf{0.0002 or } \mathbf{2 \times 10^{-4} \text{ mg/m}^3} \end{aligned}$$

The composite UF of 30 is composed of the following:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation, as data for evaluating susceptible human response are insufficient.
- UF_A: A factor of 3 ($10^{0.5}$) is applied for pharmacodynamic differences between rats and humans. No additional UF for pharmacokinetic differences is required because dosimetric equations were used to derive a $BMCL_{[HEC]}$ from the mouse exposure concentration and conditions.
- UF_D: A factor of 3 is applied because the database lacks a two-generation toxicity study by inhalation exposure.
- UF_L: A factor of 1 for extrapolation from a LOAEL to a NOAEL was applied because BMD modeling was used.

Confidence in the principal study is medium. The study (Miller et al., 1981) was well conducted, and it identifies a LOAEL for a mild occurrence of the most sensitive endpoint. Confidence in the study is medium because a NOAEL is not identified, a small number of animals were used, and there is a limited description of the nasal lesion reported. Confidence in the database is high. Subchronic inhalation studies in two species and developmental toxicity studies in two species are available and of acceptable quality. Reproductive toxicity has been studied by oral exposure. Medium confidence in the subchronic p-RfC follows.

The subchronic p-RfC of 0.0002 mg/m^3 for acrylic acid derived here is lower than the chronic RfC of 0.001 mg/m^3 available on IRIS—even though the key study and endpoint are the same. This is due to use of the BMD modeling approach to determine the POD for the subchronic p-RfC assessment, rather than the NOAEL/LOAEL approach used in the IRIS RfC assessment.

CHRONIC p-RfC

A chronic RfC of 0.001 mg/m^3 for acrylic acid is available on IRIS (U.S. EPA, 2009a), and it is based on the subchronic study in mice (Miller et al., 1981). The chronic RfC was calculated from the LOAEL of 14.9 mg/m^3 ($LOAEL_{[HEC]}$ = 0.33 mg/m^3) for degeneration of the nasal olfactory epithelium and a UF of 300 (10 for protection of sensitive individuals, 10 for interspecies extrapolation using the dosimetric adjustments for a LOAEL for a mild effect, and 3 for extrapolation from subchronic to chronic duration given rapid metabolism and limited progression of effect from short-term to subchronic exposure). This assessment was posted to IRIS on 2/17/1994.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ACRYLIC ACID

WEIGHT-OF-EVIDENCE DESCRIPTOR

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the available data for acrylic acid provide "*Inadequate Information to Assess [the] Carcinogenic Potential*." No information was located regarding carcinogenicity in humans following oral or inhalation exposure to acrylic acid. The only available animal study conducted by the oral route of exposure presents no evidence for increased tumors in rats following chronic exposure to acrylic acid in drinking water (Hellwig et al., 1993), but it appears not to have reached the

maximum tolerated dose. Dermal application studies with mice yielded negative (DePass et al., 1984) or equivocal (Hoechst-Celanese, 1990) results. Acrylic acid was clastogenic in several in vitro assays in mammalian cells (McCarthy et al., 1992; Moore et al., 1988), but it was negative in others (Wiegand et al., 1989) and in clastogenicity assays conducted in vivo (McCarthy et al., 1992). Acrylic acid did not produce point mutations in bacteria (Zeiger et al., 1987; Lijinsky and Andrews, 1980) or mammalian systems (McCarthy et al., 1992; Moore et al., 1988[1]), DNA damage in mammalian cells (McCarthy et al., 1992; Wiegand et al., 1989), or morphological transformation in mammalian cells (Wiegand et al., 1989).

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

The available data do not support derivation of oral or inhalation slope factors for acrylic acid.

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[1] The positive result in the mouse lymphoma cell assay was attributed to clastogenicity rather than point mutation by the study authors.

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APPENDIX A. BENCHMARK DOSE MODELING FOR INHALATION SUBCHRONIC P-RFC

Model Fitting Procedure for Quantal Noncancer Data

The model fitting procedure for dichotomous noncancer data is as follows. All available dichotomous models in the EPA BMDS (version 2.1) are fit to the incidence data using the extra-risk option. The multistage model is run for all polynomial degrees up to n - 1 (where n is the number of dose groups including control). Adequate model fit is judged by three criteria: 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 benchmark response (BMR). Among all the models providing adequate fit to the data, the lowest BMCL is selected as the POD when the difference between the BMCLs estimated from these models is more than 3-fold (unless it appears to be an outlier); otherwise, the BMCL from the model with the lowest AIC is chosen. In accordance with EPA (2000) guidance, benchmark concentrations (BMCs) and lower bounds on the BMC (BMCLs) associated with an extra risk of 10% are calculated for all models.

Model Fitting Results for Focal Degeneration of the Nasal Olfactory Epithelium of Female Mice (Miller et al., 1981)

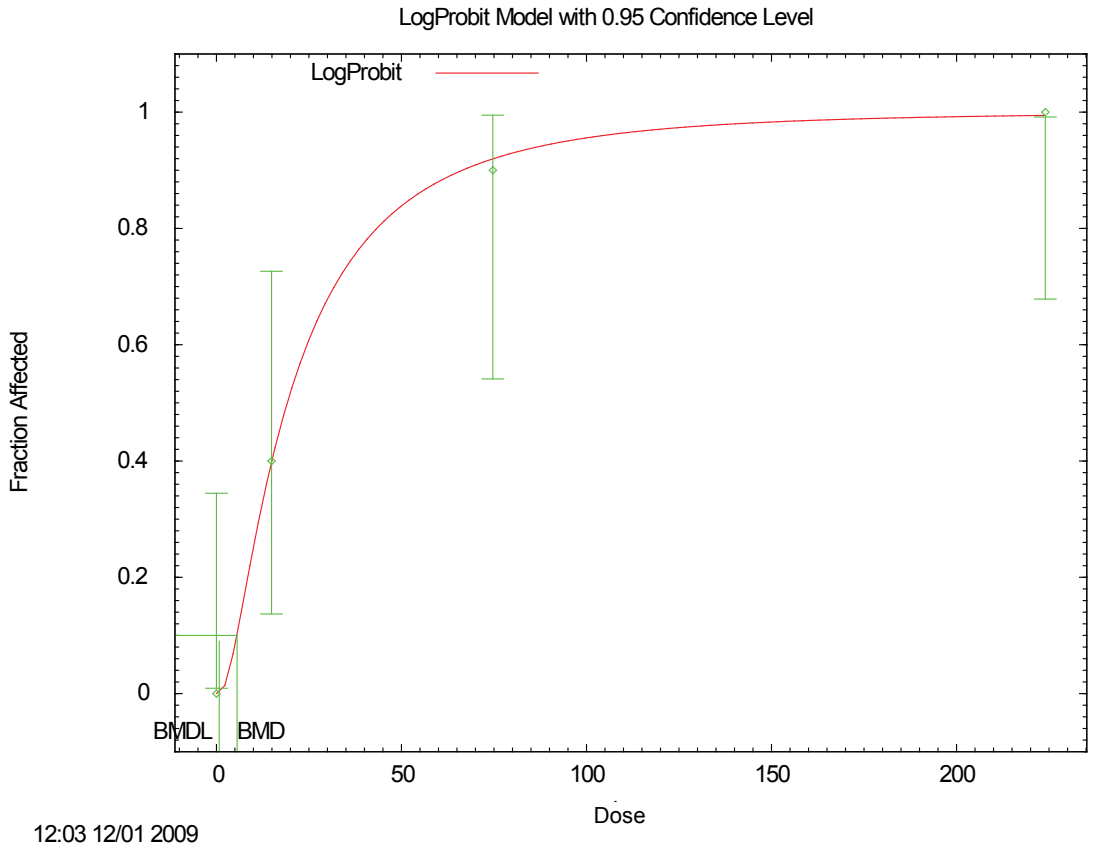
Applying the procedure outlined above to the data for focal degeneration of the nasal olfactory epithelium in female mice (Table 14), model fit was achieved with all models. Table A-1 shows the modeling results. BMCLs from models providing adequate fit differed by more than 3-fold. In accordance with EPA (2000) guidance, the lowest BMCL from a model with adequate fit has been selected for use as the POD. For this data set, the log-probit model provided the lowest BMCL (Figure A-1); the benchmark concentration (BMC_{10}) and associated 95% lower confidence limit ($BMCL_{10}$) values are 5.58 and 0.76 mg/m^3, respectively.

Table A-1. Model Predictions for Focal Degeneration of the Nasal Olfactory Epithelium in Female Mice[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[b]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	3	0.04	1.00	22.00	3.26	1.96
Logistic	2	2.65	0.27	27.67	10.76	6.09
Log Logistic[d]	2	0.2	0.91	24.28	5.63	0.97
Log Probit[d]	**2**	**0.1**	**0.95**	**24.13**	**5.58**	**0.76**
Multistage 1 degree[e]	3	0.04	1.00	22.00	3.26	1.96
Multistage 2 degree[e]	3	0.04	1.00	22.00	3.26	1.96
Multistage 3 degree[e]	2	0.04	0.98	24.00	3.29	1.97
Probit	2	2.65	0.27	27.56	10.65	6.58
Weibull[c]	3	0.04	1.00	22.00	3.26	1.96
Quantal-Linear	3	0.04	1.00	22.00	3.26	1.96

Abbreviations: AIC = Akaike Information Criterion; BMD/BMC = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL/BMCL = 95% lower confidence limit on the BMD/BMC

[a]Miller et al. (1981)
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Power restricted to ≥1
[d]Slope restricted to ≥1
[e]Betas restricted to ≥0



BMC and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg/m^3

Figure A-1. Fit of Log-Probit Model to Data on Focal Degeneration of the Nasal Olfactory Epithelium in Female Mice (Miller et al., 1981)

```
 ======================================================================
        Probit Model. (Version: 3.1;  Date: 05/16/2008)
        Input Data File:
C:\USEPA\BMDS21\Data\lnpAAFemalenonconverttoHECAAFlogprobitNONHEC.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\Data\lnpAAFemalenonconverttoHECAAFlogprobitNONHEC.plt
                                          Tue Dec 01 12:03:30 2009
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = Percent
```

```
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 250
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008



   User has chosen the log transformed model


                 Default Initial (and Specified) Parameter Values
                    background =            0
                     intercept =     -2.16744
                         slope =     0.744322


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

              intercept        slope

 intercept            1        -0.97

     slope        -0.97            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept         -3.04482          1.25617            -5.50686           -
0.582775
          slope          1.02558         0.362312            0.315466
1.7357

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -9.98095         4
   Fitted model        -10.0657         2      0.169492      2          0.9187
  Reduced model        -27.8185         1       35.6752      3         <.0001

           AIC:         24.1314


                                Goodness  of  Fit
```

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	10	0.000
14.9000	0.3919	3.919	4.000	10	0.052
74.7000	0.9161	9.161	9.000	10	-0.183
224.0000	0.9939	10.933	11.000	11	0.260

Chi^2 = 0.10 d.f. = 2 P-value = 0.9493

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 5.58051

BMDL = 0.758842

Model Fitting Results for Focal Degeneration of the Nasal Olfactory Epithelium in Male Mice (Miller et al., 1981)

Applying the procedure described above to the data for focal degeneration of the nasal olfactory epithelium in male mice (Table 14), model fit (indicated by goodness-of-fit *p*-value) was achieved with all models. Table A-2 shows the modeling results. However, further inspection revealed that model fit at the data point closest to the BMR (low-dose group) was poor (scaled residual of 1.38) for the one-degree multistage and quantal linear models, which also predicted BMC and BMCL values well below the other models. Therefore, these models have been rejected from further consideration. Among the remaining models, the BMCLs varied by less than 3-fold. In accordance with EPA (2000) guidance, the BMCL from the model with the lowest AIC was selected to use as the POD. For this data set, the 3-degree multistage model (Figure A-2) provided the lowest AIC; the resulting benchmark concentration (BMC_{10}) and associated 95% lower confidence limit ($BMCL_{10}$) are 14.36 and 3.27 mg/m^3, respectively.

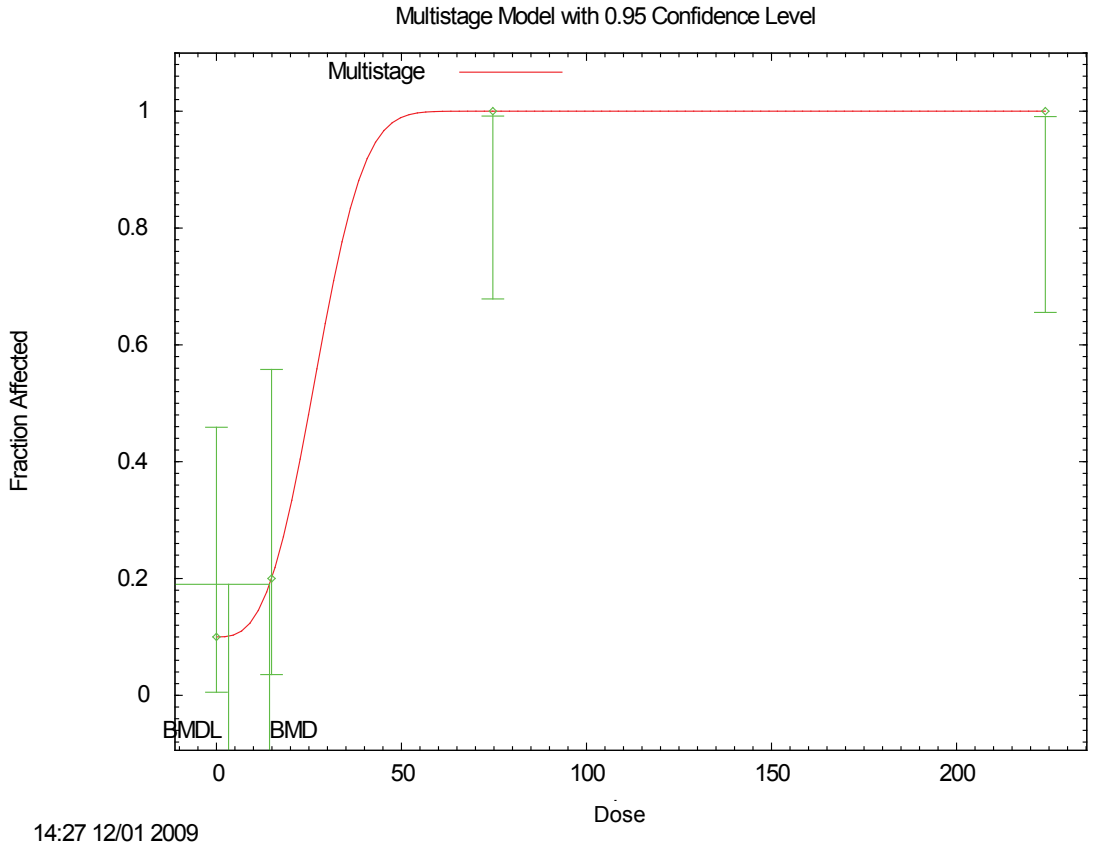
Table A-2. Model Predictions for Focal Degeneration of the Nasal Olfactory Epithelium in Male Mice[a]

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[b]	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	1	0	1.00	22.51	14.61	5.23
Logistic	2	0.34	0.84	20.92	9.81	5.26
Log Logistic[d]	1	0	1.00	22.51	14.76	7.60
Log Probit[d]	1	0	1.00	22.51	14.69	7.50
Multistage 1 degree[e]	2	3.05	0.22	24.65	3.39	1.90
Multistage 2 degree[e]	2	0.21	0.90	20.80	11.03	3.49
Multistage 3 degree[e]	**2**	**0**	**1.00**	**20.51**	**14.36**	**3.52**
Probit	2	0.33	0.85	20.88	9.25	4.97
Weibull[c]	1	0	1.00	22.51	14.37	4.67
Quantal-Linear	2	3.05	0.22	24.65	3.39	1.90

Abbreviations: AIC = Akaike Information Criterion; BMD/BMC = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL/BMCL = 95% lower confidence limit on the BMD/BMC

[a]Miller et al. (1981)
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Power restricted to ≥1
[d]Slope restricted to ≥1
[e]Betas restricted to ≥0

15



BMC and BMCLs indicated are associated with an extra risk of 10%, and are in units of mg/m^3

Figure A-2. Fit of 3-Degree Multistage Model to Data on Focal Degeneration of the Nasal Olfactory Epithelium in Male Mice (Miller et al., 1981)

```
=======================================================================
        Multistage Model. (Version: 3.0;  Date: 05/16/2008)
        Input Data File: C:\USEPA\BMDS21\Data\mstAAMaleNONHECAAMaleMultistage3.(d)
        Gnuplot Plotting File:
C:\USEPA\BMDS21\Data\mstAAMaleNONHECAAMaleMultistage3.plt
                                          Tue Dec 01 14:27:12 2009
 =======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Percent
   Independent variable = Conc

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
```

Degree of polynomial = 3

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 1
Beta(1) = 4.52028e+017
Beta(2) = 0
Beta(3) = 0

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	Background	Beta(2)	Beta(3)
Background	1	-0.079	0.015
Beta(2)	-0.079	1	-1
Beta(3)	0.015	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0.0999991	*	*	*
Beta(1)	0	*	*	*
Beta(2)	6.80291e-007	*	*	*
Beta(3)	3.55614e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-8.25485	4			
Fitted model	-8.25486	3	7.20146e-006	1	0.9979
Reduced model	-27.8185	1	39.1274	3	<.0001

AIC: 22.5097

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.1000	1.000	1.000	10	0.000
14.9000	0.2000	2.000	2.000	10	-0.000

```
   74.7000     1.0000        11.000    11.000          11        0.002
  224.0000     1.0000        10.000    10.000          10        0.000

 Chi^2 = 0.00      d.f. = 1        P-value = 0.9985


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        14.3562

            BMDL =        3.27487

            BMDU =         27.518

Taken together, (3.27487, 27.518 ) is a 90     % two-sided confidence
interval for the BMD
```