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Provisional Peer-Reviewed Toxicity Values for

Ethyl Acrylate
(CASRN 140-88-5)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGERS

Jason C. Lambert, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

Carrie Fleming, PhD
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

SRC, Inc.
7502 Round Pond Road
North Syracuse, NY 13212

PRIMARY INTERNAL REVIEWERS

Sanju Diwan, PhD
National Center for Environmental Assessment, Washington, DC

Anuradha Mudipalli, MSc, PhD
National Center for Environmental Assessment, Research Triangle Park, NC

This document was externally peer reviewed under contract to
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode-of-action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
$POD_{[ADJ]}$	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR ETHYL ACRYLATE (CASRN 140-88-5)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

Ethyl acrylate (2-propenoic acid, ethyl ester, $C_5H_8O_2$) is a colorless liquid with a penetrating acrid odor. See Figure 1 for chemical structure of ethyl acrylate. It is soluble in ethanol, ether, and chloroform and is slightly soluble in water (NTP, 1986). Ethyl acrylate is used to produce polymers and copolymers for latex paints, textiles, paper coatings and fabric finishes, and has been used as a fragrance since the 1950s. It also occurs naturally in pineapples and raspberries and has been approved by the U.S. Food and Drug Administration as a flavoring agent (NTP, 1986). A table of physicochemical properties is provided below (see Table 1).

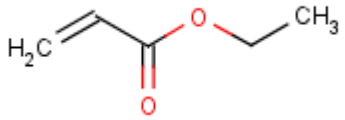


Figure 1. Chemical Structure of Ethyl Acrylate

Table 1. Physicochemical Properties Table (Ethyl Acrylate)[a]

Property (unit)	Value
Boiling point (°C)	99.8 at 760 mm Hg
Melting point (°C)	-71.2
Density (g/cm^3)	0.9234
Vapor pressure (mm Hg at 20°C)	29
Solubility in water (mg/ mL at 20°C)	10−50
Molecular weight (g/mol)	100.12
Flash point (°C)	9
Octanol/water partition coefficient (Log P)	3.5

[a]NTP (1998).

A summary of available toxicity values for ethyl acrylate (CASRN 140-88-5) from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Ethyl Acrylate (CASRN 140-88-5)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
Noncancer				
ACGIH	8-hr TLV-TWA: 5 ppm (20 mg/m^3) 15-min TLV-STEL: 15 ppm	TLVs based on upper respiratory tract, gastrointestinal, eye, and skin irritation; central nervous system impairment; and skin sensitization.	ACGIH (2013)	NA
ATSDR	NV	NA	ATSDR (2013)	NA
Cal/EPA	NV	NA	Cal/EPA (2014a)[b]	9-10-2014[b]
NIOSH	IDLH: 300 ppm	IDLH is based on toxicity data in humans (Nemec and Bauer, 1978) and animals (Oberly and Tansy, 1985; de Ceaurriz et al., 1981; Pozzani et al., 1949; Treon et al., 1949).	NIOSH (1995)	NA
OSHA	PEL: 25 ppm (100 mg/m^3)	PEL is for occupational exposure to ethyl acrylate, with skin irritation as a potential concern.	OSHA (2011; 2006)	NA
IRIS	NV	NA	U.S. EPA	9-10-2014
Drinking water	NV	NA	U.S. EPA (2012a)	NA
HEAST	NV	NA	U.S. EPA (2011a)	NA
CARA HEEP	NV	The CARA list includes a HEEP for ethyl acrylate but no RfD or RfC values.	U.S. EPA (1994a; 1987)	NA
WHO	NV	NA	WHO	9-10-2014
Cancer				
ACGIH	WOE: A4 ("*Not Classifiable as a Human Carcinogen*")	NA	ACGIH (2013)	NA
IRIS	NV	NA	U.S. EPA	9-10-2014
Drinking water	NV	NA	U.S. EPA (2012a)	NA
HEAST	OSF: 4.8 × 10^{-2} (mg/kg-d)$^{-1}$ IUR: 1.4 × 10^{-6} µg/L WOE: B2 ("*Probable Human Carcinogen*")	Cites HEEP (U.S. EPA, 1987) as the source of these values. The OSF was based on an increased incidence of squamous cell papillomas/carcinomas of the forestomach in male rats (NTP, 1986).	U.S. EPA (2011a)	NA

Table 2. Summary of Available Toxicity Values for Ethyl Acrylate (CASRN 140-88-5)

Source/Parameter[a]	Value (Applicability)	Notes	Reference	Date Accessed
IARC	WOE: Group 2B ("*Possibly Carcinogenic to Humans*")	Based on sufficient evidence of carcinogenicity in experimental animals	IARC (1999; 1986)	NA
NIOSH	REL: "Ca" ("*Potential Occupational Carcinogen*"; exposure should be limited to the lowest feasible concentration)	NA	NIOSH (2010)	NA
NTP	NV	NTP (1986) concluded that ethyl acrylate was carcinogenic to the forestomach of rats and mice in their studies, but the chemical was delisted during development of the *11th Report on Carcinogens* (NTP, 2005) and remains delisted in the *12th Report on Carcinogens* (NTP, 2011).	NTP (2011; 2005)	NA
Cal/EPA	*"Known to the State [of California] to Cause Cancer"*	NA	Cal/EPA (2014b; 2011)[b]	9-10-2014[b]

[a]Sources: American Conference of Governmental Industrial Hygienists (ACGIH); Agency for Toxic Substances and Disease Registry (ATSDR); California Environmental Protection Agency (Cal/EPA); National Institute for Occupational Safety and Health (NIOSH); Occupational Safety and Health Administration (OSHA); Chemical Assessments and Related Activities (CARA); Health and Environmental Effects Profile (HEEP); World Health Organization (WHO); Integrated Risk Information System (IRIS); Health Effects Assessment Summary Tables (HEAST); International Agency for Research on Cancer (IARC); National Toxicology Program (NTP).
[b]The Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database (http://oehha.ca.gov/tcdb/index.asp) was also reviewed and found to contain no information on ethyl acrylate.

IDLH = immediately dangerous to life or health; IUR = inhalation unit risk; NA = not applicable; NSRL = no significant risk level; NV = not available; OSF = oral slope factor; PEL = permissible exposure level; REL = recommended exposure level; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time weighted average.

Literature searches were conducted on sources published from 1900 through August 2014 for studies relevant to the derivation of provisional toxicity values for ethyl acrylate (CASRN 140-88-5). The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for toxicity values or exposure limits: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF PERTINENT DATA

The phrase "statistical significance," used throughout the document, indicates a *p*-value of <0.05 unless otherwise noted.

HUMAN STUDIES

Oral Exposure

Human studies on oral exposure to ethyl acrylate were not located in the literature.

Inhalation Exposure

Occupational epidemiology studies of 13,863 white male workers from two U.S. plants producing acrylic sheet were reported by Walker et al. (1991). In the Bristol, Pennsylvania plant, two cohorts were evaluated (1) the Early Bristol cohort consisting of 3,934 individuals employed between January 1, 1933, and December 31, 1945 (of which, approximately 74% employees were hired between 1941 and 1945), and (2) the Later Bristol cohort of 6,548 individuals hired between January 1, 1946, and December 31, 1986. In the Knoxville, Tennessee plant, the cohort consisted of 3,381 workers employed between January 1, 1943, and December 31, 1982. All groups were followed from the first day of employment or January 1, 1933, whichever came later. Assessment of exposure to ethyl acrylate and/or methyl methacrylate was based on job history and a job-specific exposure scale. The total exposure for each job held by each worker was estimated by multiplying the exposure intensity by the interval in days from the start to the end of employment in the job divided by 365.25. Mortality rates (from death certificates) were tabulated, and standardized mortality rates were calculated to assess whether occupational exposures were associated with increased incidences of colon and rectal cancers. In the Early Bristol cohort, an excess of mortality due to colon cancer was observed. Colon cancer-associated mortality appeared at least 20 years after the equivalent of 3 years of employment in jobs producing the highest exposure to ethyl acrylate and/or methyl methacrylate vapor and volatile byproducts of polymerization. Cancer of the rectum was also significantly increased in this cohort. However, assessment of the Later Bristol and Knoxville cohorts did not show excess mortality from either colon or rectal cancer. Quantitative levels of exposures to ethyl acrylate, methyl methacrylate, and byproducts of polymerization were not available in any cohort. No adjustment was made for confounding variables such as age, smoking, and alcohol consumption. No information was available on whether exposures associated with job categories were different between the Early and Later Bristol cohorts. The

study authors concluded that the excess of colon and rectal cancers in the Early Bristol study was unlikely to be associated with acrylate exposure.

Rohm and Haas Co (1987) reported a statistically increased incidence of respiratory cancers in the Knoxville plant workers (cohort described above) as compared with nonfactory workers. However, there was no relationship to length of employment or to job categories with the highest exposures. As noted for Walker et al. (1991), exposure was not quantified, and no adjustment was made for confounding variables. This study is not suitable for quantitative risk assessment.

A prospective cohort study on the effects of occupational exposure to chemicals (including ethyl acrylate) involved in the production of acrylic acid, acrylic acid esters and acrylate was conducted in 1992−1999 (Tucek et al., 2002). Exposure to the chemicals was determined by personal passive dosimetry. Workers (60 exposed and 60 controls) were assessed annually for general health (interview), a general medical examination, clinical chemistry (aminotransferases, ALT, AST, GMT, alkaline phosphatase, glucose, total protein, uric acid, triacylglycerols, cholesterol [total, HDL and LDL], urea, creatinine, and bilirubin), urinalysis (pH, protein, glucose, acetone, urobilinogen, sediment), hematology (automated blood count), serum immunity (immunoglobulins G, A, M, E; complements C3 and C4; lysozyme; orosomucoid; transferring; prealbumin; ceruloplasmin, alpha-1-fetoprotein; alpha-1-antitrypsin; alpha-2-macroglobulin; albumin; haptoglobin; hemopexin; C-reactive protein; rheumatoid factor; antistreptolysin-O and circulating immunocomplexes), selected tumor markers (carcinoembryonic antigen, neuron specific enolase, thymidine kinase), and spirometry. Exposures were generally found to be low (below maximum allowable concentrations values or suggested limits for each chemical). No differences were noted over the 8-year duration of the study between control and exposed groups that could be attributed to acrylate exposure.

ANIMAL STUDIES

Oral Exposure

Subchronic-duration Studies

Bernacki et al. (1987a)

In an unpublished industry study, ethyl acrylate (>99% purity) was administered in the drinking water of male and female F344 rats (40/group for males and 20/group for females) at concentrations of 0 (water control); 200, 1,000, 2,000, or 4,000 ppm, 7 days/week, for 13 weeks (Bernacki et al., 1987a). Based on the study authors' calculations, compound intake averaged 0, 17, 70, 135, and 249 mg/kg-day, for males and 0, 20, 87, 161, and 293 mg/kg-day, for females. Interim sacrifices consisted of 10 males/group after Study Weeks 1 and 2, and 10 rats/sex/group after Study Week 4. Samples of drinking water were analyzed for ethyl acrylate concentrations and did not differ significantly from target concentrations. Animals were observed twice daily for mortality and morbidity during the week and once daily on weekends and holidays. Livers and kidneys were weighed at the 4- and 13-week sacrifices. At all necropsy intervals, the entire stomach was removed, weighed, dissected free of other tissues, and opened along the greater curvature, weighed, and fixed for staining and analysis. The following tissues from all rats were preserved similarly: liver, kidneys, heart, adrenals, thyroid/parathyroid, spleen, gonads, esophagus (only at 13 weeks), and gross lesions. Histopathology was performed on hematoxylin- and eosin-stained sections of both the forestomach and glandular stomach and on gross lesions from all dose groups.

No deaths or clinical signs of toxicity were reported (Bernacki et al., 1987a). Male body weights were significantly decreased in all treatment groups (4, 9, 15, and 17% less than controls from low through high doses, respectively; $p < 0.05$), whereas there were no changes in female body weight throughout the study. Food consumption was decreased in males from all treated groups throughout the study and in females receiving ≥87 mg/kg-day. A dose-dependent decrease in water consumption (~20−40% less than controls, $p < 0.05$) was observed in both sexes. The study authors considered the effects on male body weights to be secondary to decreased drinking water and unrelated to treatment. However, it is not clear whether the treatment-related changes in water consumption resulted from unpalatability, or whether they may have been related to irritation of the stomach, as described below. Dose- and time-related changes in both absolute and relative stomach weights were noted at all necropsy intervals. After Week 1, absolute and relative stomach weights were increased in the high-dose male group. Following Week 2, relative stomach weights—but not absolute stomach weights—were increased at concentrations ≥70-mg/kg-day male group. After Week 4, increases in relative stomach weights were observed in females at ≥87 mg/kg-day and males at ≥135 mg/kg-day, while increases in absolute stomach weight occurred at the high dose in both sexes. At terminal sacrifice, increased relative stomach weights were observed in males at ≥70 mg/kg-day and females at ≥161 mg/kg-day, while absolute stomach weights were elevated in females at ≥161 mg/kg-day and males only at 249 mg/kg-day. No changes in stomach weight were observed in either sex at any sacrifice in the low dose group. Changes in liver and kidney weights, noted at 4 and 13 weeks, were small in magnitude and lacked a dose-response relationship; the study authors considered these findings to be secondary to body-weight changes and not toxicologically significant.

Gross pathology was observed only in the forestomach after 1, 2, and 4 weeks of treatment (Bernacki et al., 1987a). After Weeks 1 and 2, findings consisted of focal/multifocal discolorations in a small number of rats in the two highest dose groups. After Week 4, "prominence" and/or thickening of the limiting ridge of the forestomach was noted at ≥87 mg/kg-day in females (2/10, 2/10, and 7/10 in the 87-, 161-, and 293-mg/kg-day groups, respectively) and ≥135 mg/kg-day in males (3/10 and 5/10 in the 135- and 249-mg/kg-day groups, respectively). No gross pathology was observed in controls or at the lowest dose at any interim sacrifice interval. At terminal sacrifice, no gross pathology was observed in any treatment group. However, histopathological analysis showed a diffuse hyperplasia of the squamous epithelium of the forestomach at all time intervals, generally in a dose-related manner, at exposure concentrations ≥1,000 ppm in both sexes (70 mg/kg-day in males and 87 mg/kg-day in females), with no apparent sex difference at 4 or 13 weeks. Severity of the hyperplasia ranged from minimal to moderate at the highest dose and was minimal at 1,000 ppm. Hyperplasia was characterized as basal cell hyperplasia with an increase in number and size of basophilic cells, arranged in a disorganized fashion. Hyperkeratosis of the forestomach occurred at ≥2,000 ppm (135 mg/kg-day in males and 161 mg/kg-day in females) at all time intervals, generally in conjunction with hyperplasia. The study authors reported that gross thickening of the forestomach and/or limiting ridge generally corresponded to diffuse hyperplasia and/or hyperkeratosis histologically. Histopathology findings in the forestomach at terminal sacrifice are reported in Table 3. No significant gross pathology or histopathology in the glandular stomach was observed at any concentration. Based on increased stomach weight and histopathology in the forestomach of both males and females, as well as decreased body weight in males, the NOAEL was 200 ppm (17 mg/kg-day in males), and the LOAEL was 1,000 ppm (70 mg/kg-day in males).

Table 3. Incidences of Forestomach Lesions in F344/N Rats Treated with Ethyl Acrylate in Drinking Water for 13 Weeks

Parameter	Control	17 mg/kg-d (200 ppm)	70 mg/kg-d (1,000 ppm)	135 mg/kg-d (2,000 ppm)	249 mg/kg-d (4,000 ppm)
Males					
Hyperplasia, diffuse					
Minimal	0/10[a]	0/10	8/10[b]	2/10	3/10
Mild	0/10	0/10	0/10	8/10[b]	6/10[b]
Moderate	0/10	0/10	0/10	0/10	1/10
Total number affected	0/10	0/10	8/10[b]	10/10[b]	10/10[b]
Hyperkeratosis	0/10	0/10	0/10	10/10[b]	10/10[b]
Females					
Parameter	**Control**	**20 mg/kg-d (200 ppm)**	**87 mg/kg-d (1,000 ppm)**	**161 mg/kg-d (2,000 ppm)**	**293 mg/kg-d (4,000 ppm)**
Hyperplasia, diffuse					
Minimal	1/10	0/10	6/10[b]	9/10[b]	2/10
Mild	0/10	0/10	0/10	1/10	5/10[b]
Moderate	0/10	0/10	0/10	0/10	3/10
Total number affected	1/10	0/10	6/10[b]	10/10[b]	10/10[b]
Hyperkeratosis	0/10	0/10	1/10	4/10[b]	10/10[b]

[a]Number affected/number examined.
[b]Significantly different from control at $p < 0.05$ based on Fisher's exact test performed for this review.

Source: Bernacki et al. (1987a).

Bernacki et al. (1987b)

A second study using gavage dosing was also performed (Bernacki et al., 1987b). Ethyl acrylate (>99% purity) was administered via gavage to male F344 rats (20/group) at concentrations of 0, 0.4%, 2%, or 4% in corn oil, resulting in doses of 0, 20, 100, or 200 mg/kg, respectively, for 5 days/week, for 13 weeks. Doses adjusted to a continuous exposure were 0, 14, 71, and 143 mg/kg-day). An additional 10 rats were treated with 200-mg/kg ethyl acrylate for the first 4 weeks of the study and then were placed in a recovery group (corn oil only) for the remaining 9 weeks of the study. An interim sacrifice of 10 males/group occurred after Week 4. Animals were observed twice daily on treatment days and once daily on weekends and holidays for mortality and morbidity. Body weights and food consumption were recorded once weekly. Livers and kidneys were weighed at the 4- and 13-week sacrifices. At the same time, the entire stomach was removed, weighed, dissected free of other tissues and opened along the greater curvature, weighed, and fixed for staining and analysis. The following tissues from all rats were preserved similarly: liver, kidneys, heart, adrenals, thyroid/parathyroid, spleen, gonads, and gross lesions. Histopathology was performed on hematoxylin- and eosin-stained sections of both the forestomach and glandular stomach and on gross lesions from all dose groups.

No deaths or clinical signs of toxicity were reported (Bernacki et al., 1987b). Body weights were significantly decreased at the end of the study in the 71-mg/kg-day, 143-mg/kg-day, and recovery groups (2.5, 7.3, and 2.5% less than controls, respectively; $p < 0.05$). There were no treatment-related changes in food consumption during the study. Dose- and time-related changes in both absolute and relative stomach weights were noted at the 4- and 13-week necropsy intervals. After Week 4, absolute and relative stomach weights were increased in the 71-mg/kg-day (28 and 24%, respectively) and the 143-mg/kg-day (41 and 44%, respectively) groups. At terminal sacrifice, increased absolute and relative stomach weights were observed in the 14-mg/kg-day (7 and 9%, respectively), the 71-mg/kg-day (26 and 30%, respectively), and the 143-mg/kg-day (50 and 63% respectively) groups. No changes in stomach weight were observed at either sacrifice in the recovery group. Changes in liver and kidney weights were small in magnitude and lacked a dose-response relationship; the study authors did not consider these findings to be toxicologically significant.

Gross pathology was observed only in the forestomach after 4 and 13 weeks of treatment in the 71- and 143-mg/kg-day groups (Bernacki et al., 1987b). After Week 4, thickening of the forestomach (1/10 rats) and raised or discolored foci (4/10 rats) were observed in the 143-mg/kg-day group. Also, prominence of the limiting ridge was observed in the 71-mg/kg-day group (6/10 rats) and the 143-mg/kg-day groups (10/10 rats). No gross pathology was observed in controls or the 14-mg/kg-day group at 4 weeks. At terminal sacrifice, changes in the forestomachs of the 143-mg/kg-day group included thickening (1/10), irregular surface (1/10), raised plaques (5/10), nodules (2/10), enlarged stomach (2/10), and prominence of the limiting ridge (9/10). The only change noted in the 71-mg/kg-day group was prominence of the limiting ridge (1/10), and no changes were observed in the control, 14-mg/kg-day, or recovery groups. Changes in the small intestine were observed in all groups and consisted of white thickened walls with prominent Peyer's patches and fluid content; these changes were considered to be related to repeated dosing with corn oil and were not due to ethyl acrylate.

Histopathological changes in the forestomachs of treated rats were generally varied in a dose-related manner; no changes were noted in the recovery group. Diffuse hyperplasia of the squamous epithelium of the forestomach was observed at 14, 71, and 143 mg/kg-day at all time intervals, generally in a dose-related manner. Severity of the hyperplasia ranged from minimal at 14 mg/kg-day to mild at 71 mg/kg-day and moderate at 143 mg/kg-day. Hyperplasia was characterized as basal cell hyperplasia and generally occurred at a comparable severity in conjunction with diffuse hyperkeratosis at 71 and 143 mg/kg-day. Other changes noted were submucosal inflammation at 71 and 143 mg/kg-day, focal submucosal edema at 71 and 143 mg/kg-day, and focal papillomatous hyperplasia at 143 mg/kg-day. The study authors reported that gross thickening of the forestomach and/or limiting ridge generally corresponded to diffuse hyperplasia and/or hyperkeratosis histologically. Histopathology findings at terminal sacrifice are reported in Table 4. No significant compound-related gross pathology or histopathology in the glandular stomach was observed. Based on hyperplasia in the forestomach, the LOAEL was 14 mg/kg-day, and no NOAEL was available.

Table 4. Incidences of Forestomach Lesions in male F344/N Rats Treated with Ethyl Acrylate by Gavage for 13 Weeks

Parameter	Control	20 mg/kg (14 mg/kg-d)[a]	100 mg/kg (71 mg/kg-d)[a]	200 mg/kg (143 mg/kg-d)[a]	Recovery[b]
Hyperplasia, diffuse					
Minimal	0/10[c]	4/10	1/10	0/10	0/10
Mild	0/10	1/10	9/10[d]	2/10	0/10
Moderate	0/10	0/10	0/10	8/10[d]	0/10
Total number affected	0/10	5/10[d]	10/10[d]	10/10[d]	0/10
Hyperkeratosis, diffuse	0/10	0/10	10/10[d]	10/10[d]	0/10
Hyperplasia, papillomatous, focal					
Marked	0/10	0/10	0/10	4/10	0/10
Severe	0/10	0/10	0/10	5/10[d]	0/10
Total number affected	0/10	0/10	0/10	9/10[d]	0/10
Hyperkeratosis, focal	0/10	0/10	0/10	9/10[d]	0/10
Submucosal inflammation	0/10	0/10	0/10	9/10[d]	0/10
Submucosal edema, focal	0/10	0/10	1/10	9/10[d]	0/10

[a]Administered dose (duration-adjusted dose; adjusted to continuous exposure as follows: $DOSE_{ADJ}$ = DOSE × exposure d/7 d).
[b]Received 200-mg/kg ethyl acrylate for the first 4 wk, then corn oil for the remaining 9 wk of exposure.
[c]Number affected/number examined.
[d]Significantly different from control at $p < 0.05$ based on Fisher's exact test performed for this review.

Source: Bernacki et al. (1987b).

NTP (1986)

Three, 13-week studies were conducted by NTP (1986) to evaluate the subchronic toxicity of ethyl acrylate by gavage exposure: one in F344 rats and two in $B6C3F_1$ mice. In the rat study, ethyl acrylate (≥99% purity) in corn oil was administered via gavage (10 rats/sex/group) at doses of 0 (vehicle control), 7, 14, 28, 55, or 110 mg/kg-day, for 5 days/week, for 13 weeks. Doses adjusted to a continuous exposure were 5, 10, 20, 39, and 79 mg/kg-day. Animals were checked for mortality and signs of morbidity twice daily. Each animal was given a clinical examination weekly, including palpation for tissue masses. Body-weight data were collected weekly. Animals surviving to the end of the 91-day study were euthanized. Gross necropsies were performed on all animals, including those that died or were sacrificed in extremis during the study. Histopathology was performed only in the control and high-dose groups for the following organs: gross lesions, skin, mandibular and mesenteric lymph nodes, mammary gland, salivary gland, thigh muscle, bone marrow, thymus gland, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach (forestomach and glandular), small intestine, cecum, colon, liver, pancreas, spleen, kidneys, urinary bladder, testes or ovaries, prostate or uterus, brain, and pituitary gland.

No mortality or clinical signs of toxicity occurred during the study, and mean body weights of dosed animals were comparable to controls. The only observed gross findings were erythema in the duodenum of 1/10 males at the high dose of 79 mg/kg-day and "prominent" blood vessels in the cardiac region of the stomach in 2/10 males at 79 mg/kg-day. Treatment-related histopathology was not observed in the high-dose group as compared with controls. The NOAEL of this rat study was considered to be 79 mg/kg-day, the highest dose tested, and a LOAEL could not be identified.

In the first mouse study, ethyl acrylate (≥99% purity) was administered via gavage in corn oil (10/sex/group) at doses of 0 (vehicle control), 1.5, 3, 6, 12, or 25 mg/kg-day, for 5 days/week, for 13 weeks (NTP, 1986). The second study was conducted at higher doses (0, 12, 25, 50, or 100 mg/kg-day) because no treatment-related effects were observed in the first study. Duration adjusted doses were 0, 1, 2, 4, 9, and 18 mg/kg-day for the first experiment and 0, 9, 18, 36, and 71 mg/kg-day for the second experiment. Experimental protocols for these studies were the same as for the rat study. In the first mouse study, 2/10 females and 1/10 males given 18 mg/kg-day and 1/10 female given 4 mg/kg-day died. The male mouse was accidentally killed, and the causes of death of the female mice could not be determined. In the second study, no treatment-related mortality was observed. The mortality in the first study was, therefore, considered to be incidental to treatment. Mean body weights were comparable between dosed and control animals in both studies. No treatment-related gross or microscopic histopathology in the high-dose group, relative to controls, was observed. Combining the findings in both studies, the NOAEL was identified as 71 mg/kg-day, the highest dose tested, and a LOAEL could not be determined.

Ghanayem et al. (1991c)

As part of a series of stop-recovery studies designed to elucidate mechanisms of pathogenesis in the rat forestomach, Ghanayem et al. (1991c) administered ethyl acrylate (>99% purity) via gavage in corn oil vehicle to male F344 rats treated with 0- (vehicle control), 100-, or 200-mg/kg-day ethyl acrylate, for 5 days/week, for 13 weeks (0, 71, and 143 mg/kg-day, duration adjusted). Representative samples of rats from each dose group (10−11/group) were euthanized at 24 hours, 8 weeks, and 19 months following the last dose. Only the forestomach, glandular stomach, and liver were examined grossly and histopathologically. At the first sacrifice, no gross or microscopic changes were observed in the glandular stomach or liver, but dose-related effects were observed in the forestomach. In the 71-mg/kg-day group, a thickening of the forestomach, accompanied by moderate mucosal hyperplasia, was found in all treated animals (10/10) as compared with 0/10 in the vehicle control. In the 143-mg/kg-day group, randomly distributed focal and multifocal lesions with hyperplastic proliferations of the mucosa were observed in all treated animals (11/11). Following an 8-week recovery period, there was a significant decline in the incidence and severity of forestomach mucosal hyperplasia in both dose groups, with most animals showing grossly and histologically normal mucosa. However, equal to minimal hyperplasia was still observed in a small number of rats. Following 19 months of recovery, the forestomachs of rats in both dosed groups were grossly normal with the exception of an occasional, more opaque forestomach in the high-dose animals. Approximately one-third of animals treated with 143 mg/kg-day had minimal focal or multifocal areas of residual hyperplasia in the mucosa; these findings were occasionally accompanied by localized mild submucosal inflammation. The LOAEL for this study was 71 mg/kg-day, based on forestomach histopathology, and a NOAEL could not be determined.

Chronic-duration Studies

NTP (1986)

Groups of F344 rats (50/sex/dose group) were administered ethyl acrylate (≥99% purity) by gavage in corn oil at daily doses of 0 (vehicle control), 100, or 200 mg/kg-day, for 5 days/week, for 103 weeks (NTP, 1986). Duration adjusted doses were 0, 71, and 143 mg/kg-day. All animals were observed twice daily for mortality and morbidity. Body weights were recorded once per week for the first 12 weeks and monthly thereafter. Moribund animals and those surviving to the end of the study were sacrificed with carbon dioxide and necropsied. Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically in all groups: tissue masses, gross lesions, abnormal lymph nodes, blood smears, mandibular or mesenteric lymph nodes, mammary gland, salivary gland, bone marrow, femur, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach (forestomach and glandular stomach), small intestine, colon, liver, pancreas, spleen, kidneys, adrenals, urinary bladder, prostate and testes or ovaries and uterus, brain, pituitary, eyes, ears, nasal cavity, larynx, sciatic nerve, rectum, thigh muscle, and skin.

No significant differences in survival were observed between groups of the same sex (NTP, 1986). Two low-dose males, one high-dose male, and one high-dose female were accidentally killed. Clinical signs of toxicity and body weights were similar between dosed groups and controls. The only reported nonneoplastic lesions occurred in the forestomach of both males and females and were dose related (see Table 5). These lesions included inflammation, epithelial hyperplasia, and hyperkeratosis. Squamous epithelial hyperplasia of the forestomach was characterized by increased basophilia and mitotic activity of the basal epithelium and an overall increase in the number of epithelial cells. Hyperkeratosis usually accompanied the hyperplasia. Increased cellularity of the squamous epithelium often resulted in a grossly wrinkled appearance of the mucosa. At times, the mucosa was disorganized to the extent that masses of keratin, cellular debris, food particles, and hair were trapped in epithelial invaginations within the wall of the forestomach. Foreign material (hair) was sometimes found in the submucosa adjacent to these masses and was often accompanied by an inflammatory reaction. Based on forestomach lesions, the LOAEL was 71 mg/kg-day, and a NOAEL could not be identified.

Neoplasms were only observed in the forestomach (NTP, 1986). These findings are presented in Table 5. Statistically significant positive trends were observed in the incidences of male rats with squamous cell papillomas and squamous cell carcinomas ($p < 0.01$); the incidences in the dosed groups were significantly higher than those in the vehicle controls. In females, squamous cell papillomas occurred with a significantly positive trend, and the incidence in the high-dose group was significantly higher relative to controls. A small increase (2/50 animals) in the incidence of squamous cell carcinomas was observed in the high-dose females as compared with controls (0/50 animals); the difference was not statistically significant. Other tumor findings in other target organs were considered by the study authors to be typical of aging rats and unrelated to ethyl acrylate exposure.

Table 5. Incidences of Forestomach Nonneoplastic and Neoplastic Lesions in F344/N Rats Treated with Ethyl Acrylate by Gavage for 103 Weeks

Parameter	Control	100 mg/kg (71 mg/kg-d)[e]	200 mg/kg (143 mg/kg-d)[e]
Males			
Nonneoplastic lesions			
Hyperkeratosis	0/50[a]	37/50[b]	46/50[b]
Epithelial hyperplasia	1/50	41/50[b]	46/50[b]
Acute and/or chronic inflammation	1/50	8/50[b]	28/50[b]
Neoplastic lesions			
Squamous cell papilloma	1/50[c]	15/50[d]	29/50[d]
Squamous cell carcinoma	0/50[c]	5/50[d]	12/50[d]
Squamous cell papilloma or carcinoma	1/50[c]	18/50[d]	36/50[d]
Females			
Nonneoplastic lesions			
Hyperkeratosis	0/50	24/50[b]	46/50[b]
Epithelial hyperplasia	0/50	34/50[b]	49/50[b]
Acute and/or chronic inflammation	1/50	3/50	20/50[b]
Neoplastic lesions			
Squamous cell papilloma	1/50[c]	6/50	9/50[d]
Squamous cell carcinoma	0/50	0/50	2/50
Squamous cell papilloma or carcinoma	1/50[c]	6/50	11/50[d]

[a]Number affected/number examined.
[b]Significantly different from control at $p < 0.05$ based on Fisher's exact test performed for this review.
[c]Statistically significant trend at $p < 0.01$ as reported by researchers.
[d]Significantly different from control at $p < 0.05$ based on Fisher's exact test as reported by researchers.
[e]Administered dose (duration-adjusted dose; adjusted to continuous exposure as follows: $DOSE_{ADJ}$ = DOSE × exposure d/7d).

Source: NTP (1986).

In the same laboratory, groups of $B6C3F_1$ mice (50/sex/dose group) were administered ethyl acrylate (≥99% purity) by gavage in corn oil at daily doses of 0 (vehicle control), 100, or 200 mg/kg-day for 5 days/week for 103 weeks (NTP, 1986). Duration adjusted doses were 0, 71, and 143 mg/kg-day. Dosing regimen, experimental protocol, and statistical analysis were the same as those for the chronic-duration rat study, except that in mice, the gall bladder was examined histopathologically in addition to other target tissues.

No significant differences in survival were observed between any groups of the same sex (NTP, 1986). Three vehicle control, one low-dose, and eight high-dose males, and three vehicle control and three high-dose females were accidentally killed. Mean body weights of males were comparable between treated and control groups. In females, mean body weights of low-dose animals, but not high-dose animals, were decreased relative to controls. The incidences of

nonneoplastic lesions in the forestomach were dose related in both male and female mice (see Table 6). These lesions included hyperkeratosis, ulceration, inflammation, and epithelial hyperplasia. Epithelial hyperplasia of the forestomach was manifested by increased cellular basophilia, elongation, and proliferation of basilar cells with increased mitotic activity, and increased thickness of the squamous epithelium without folding of the underlying musculature. Mild epithelial downgrowth was present in some cases. Epithelial hyperplasia was usually associated with variable degrees of hyperkeratosis. These findings were less frequent in mice than in rats. Pyogenic (producing pus) infection of female genital organs occurred in mice late in the study (after Week 86) but was not compound related (11/50, 12/50, and 11/50 in the control, low-, and high-dose groups, respectively). Although an etiologic agent for these findings was not identified for this study, identical lesions observed in later studies in the same laboratory were attributed to a bacterial infection (*Klebsiella oxytoca*). Based on forestomach lesions, the LOAEL for this study was 71 mg/kg-day, the lowest dose tested, and a NOAEL could not be identified.

Treatment-related neoplasms occurred only in the mouse forestomach (NTP, 1986). These findings are presented in Table 6. Statistically significant positive trends occurred in the incidences of male mice with squamous cell papillomas, squamous cell carcinomas, or combined papillomas or carcinomas. The incidences of these tumors were statistically significantly elevated in the high-dose group, and marginally so in the low-dose combined group ($p = 0.03$ by Fisher's exact test, but $p = 0.06$ in life table and incidental tumor tests), relative to vehicle controls. In females, the combined incidences of squamous cell papillomas and carcinomas showed a significantly positive trend, and the incidence at the high dose, but not the low dose, was significantly increased as compared to controls. Other tumors in other target organs were considered by the researchers to be typical of aging mice and unrelated to ethyl acrylate treatment.

Ghanayem et al. (1994)

In a stop-recovery design study, Ghanayem et al. (1994) evaluated the effects of chronic-duration gavage dosing with ethyl acrylate (99% purity). Male F344 rats were treated with a gavage dose of 0 (vehicle control) or 200 mg/kg-day (5 days/week) for 6 or 12 months (duration adjusted doses were 0 and 143 mg/kg-day), and groups of 5 rats were sacrificed at various intervals following termination of exposure (immediately, and 2 and 15 months postdosing for the 6-month treatment group; immediately, and 2 and 9 months postdosing for the 12-month group) for evaluation of forestomach and liver histopathology. Cell proliferation (S-phase nuclei during replicative DNA synthesis) was assessed in all groups receiving ethyl acrylate or corn oil vehicle for up to 12 months and after 2- or 9-month recovery periods, using BrDU incorporation via subcutaneous implantation of osmotic minipumps. No other endpoints were evaluated. A sustained increase in forestomach histopathology occurred with treatment, with the severity of lesions increasing with exposure duration. Animals treated for 6 months and given 2 or 15 months of recovery showed a time-dependent regression of cell proliferation and hyperplasia and did not develop forestomach neoplasms (Ghanayem et al., 1994). In contrast, although significant decreases in the forestomach hyperplasia/cell proliferation were observed in rats treated for 12 months and given 2 months of recovery (relative to those examined immediately after 12 months of treatment), two of five of these animals developed squamous cell papillomas. Animals treated for 12 months and given 9 months of recovery exhibited squamous cell carcinomas (3/13) and papillomas (1/13) with a combined incidence of 4/13. In animals treated for 12 months, a marked increase in cell proliferation in forestomach squamous and basal

epithelium cells was observed in the animals; the study authors considered morphological evidence of increased hyperplasia as indicative of increased epithelial cell proliferation. No lesions, increased cell proliferation, or tumors were observed in the liver. Based on severe forestomach histopathology at the end of exposure, the LOAEL was 143 mg/kg-day, and a NOAEL could not be identified.

Table 6. Incidences of Forestomach Nonneoplastic and Neoplastic Lesions in B6C3F$_1$ Mice Treated with Ethyl Acrylate by Gavage for 103 Weeks

Parameter	Control	100 mg/kg (71 mg/kg-d)[e]	200 mg/kg (143 mg/kg-d)[e]
Males			
Nonneoplastic lesions			
Hyperkeratosis	0/48[a]	19/47[b]	28/50[b]
Epithelial hyperplasia	0/48	17/47[b]	26/50[b]
Acute and/or chronic inflammation	0/48	3/47	8/50[b]
Ulceration	2/48	1/47	5/50
Neoplastic lesions			
Squamous cell papilloma	0/48[c]	4/47	9/50[d]
Squamous cell carcinoma	0/48[c]	2/47	5/50[d]
Papilloma or carcinoma	0/48[c]	5/47[d]	12/50[d]
Females			
Nonneoplastic lesions			
Hyperkeratosis	2/50	14/49[b]	32/48[b]
Epithelial hyperplasia	3/50	12/49[b]	30/48[b]
Acute and/or chronic inflammation	1/50	4/49	12/48[b]
Ulceration	0/50	1/49	6/48[b]
Neoplastic lesions			
Squamous cell papilloma	1/50	4/49	5/48
Squamous cell carcinoma	0/50	1/49	2/48
Papilloma or carcinoma	1/50[c]	5/49	7/48[d]

[a]Number affected/number examined.
[b]Significantly different from control at $p < 0.05$ based on Fisher's exact test performed for this review.
[c]Statistically significant trend at $p < 0.05$ as reported by researchers.
[d]Significantly different from control at $p < 0.05$ based on Fisher's exact test as reported by researchers.
[e]Administered dose (duration-adjusted dose; adjusted to continuous exposure as follows: $DOSE_{ADJ}$ = DOSE × exposure d/7d).

Source: NTP (1986).

Borzelleca et al. (1964)

Wistar rats (25/sex/group) were administered ethyl acrylate (purity not reported) in drinking water for 104 weeks (Borzelleca et al., 1964). Exposures in the low- and mid-dose

groups were to concentrations of 6 and 60 ppm for the first 4 months, and then 7 and 70 ppm for the remaining 20 months; the high exposure group was maintained at 2,000 ppm throughout the study, and the control group received untreated water. Doses of 0, 0.5, 5, and 120 mg/kg-day (males) and 0, 0.7, 7, and 180 mg/kg-day (females) are estimated using body weights and fluid consumption rates reported in the study. Because fluid consumption was reported as an average over the duration of the study while body weights were reported for a number of unevenly spaced time points (1, 3, 6, 13, 26, 52, 78, and 104 weeks), average body weight over the course of the study was calculated as a time-weighted mean of the given time points. There was no 4-month-time point, so the 1−13-week-time points were assumed to receive 6 or 60 ppm, and the 26−104-week-time points were assumed to receive 7- or 70-ppm ethyl acrylate. Drinking water bottles were structurally modified to reduce ethyl acrylate volatilization, and tests showed essentially no loss of ethyl acrylate from the drinking water bottles. For the study, stock solutions of the monomers were prepared in tightly stoppered carboys once a week, and the drinking water bottles were filled twice a week, with water remaining in the bottles at refilling being discarded. Animals were individually caged and weighed weekly. Drinking water consumption was determined over a 3-day period at the end of Study Weeks 1 and 4, monthly through 6 months, and on even months thereafter. Food consumption was measured over 3-day periods at the same time intervals. Hematologic end points (hematocrit, hemoglobin, total and differential white cell counts) were determined from 5 rats/sex/group at 3-month intervals. Semi-quantitative tests for the urinary concentrations of reducing substances and protein were performed on urine pooled from 5 rats/sex/group at 3-month intervals. At sacrifice, relative organ weights were calculated for heart, spleen, kidney, liver, and testes. Histopathology was conducted on animals surviving to the end of the study and those dying during the study (if not autolyzed) in controls and in the mid- and high-dose groups. The following tissues were examined grossly: heart, lung, liver, kidney, urinary bladder, spleen, gastroenteric (organs not defined), skeletal muscle, bone marrow, skin, brain, thyroid, adrenal, pancreas, pituitary, and gonads. Histopathology was not conducted on the low-dose groups.

No treatment-related mortality was observed relative to controls (Borzelleca et al., 1964). Female body weights from the 180-mg/kg-day exposure group were significantly decreased throughout the study (15% less than controls at termination, $p < 0.05$). Male body weights were only significantly reduced during the first year of the study and in the highest exposure group (120 mg/kg-day) and were within 10% of control weights during this time. Significantly decreased drinking water consumption (20−25% less than controls) was observed throughout the study at the high dose in both males and females. Overall food consumption was significantly decreased only in high-dose females (12% less than controls, $p < 0.05$). All hematological values were within normal ranges in all groups throughout the study. Similarly, urinary concentrations of protein and reducing substances showed no dose-related trends. No effects of treatment were observed at any dose level for relative organ weights as compared with those of controls. Histopathologic findings showed no abnormalities or lesions, including neoplasms, in any dosed group other than those occurring in aging rats of this strain. The LOAEL for this study was 180 mg/kg-day for body-weight decrements of ≥10% in females; the NOAEL was 7 mg/kg-day.

Purebred beagle dogs (2/sex/group) were administered ethyl acrylate (purity not reported) dissolved in corn oil and administered in gelatin capsules (Borzelleca et al., 1964). The doses were reported as dietary equivalents of 0, 10, 100, and 1,000 ppm feed (estimated to be equivalent to daily doses of 0, 0.20, 2.0, and 23 mg/kg-day, based on average measured body weight and default food consumption), for 7 days/week, for 104 weeks. All animals in the

high-dose group vomited following the first administration of ethyl acrylate capsules. When doses were reduced to 500 ppm (11 mg/kg-day), 2/4 animals vomited. Dosing was discontinued for the remainder of the first week and restarted at a dietary equivalent of 300 ppm (6.8 mg/kg-day), which was retained by all animals. Following a step-wise increase of the dose to 1,000 ppm (23 mg/kg-day) over the first 16 weeks, the high dose was retained by the animals and administered at this concentration for the remainder of the study. Average daily dose at the high dose was 22 mg/kg-day after adjusting for the first 16 weeks (and assuming a steady increase from weeks 1 to 16). Animals were individually caged and weighed weekly. Food consumption was measured daily. Hematologic endpoints (hematocrit, hemoglobin, total and differential white cell counts) were measured in all dogs prior to initiation of treatment, at 2, 4, and 13 weeks, and at 3-month intervals thereafter. Pooled urine concentrations (2/sex/group) of reducing substances and protein were assessed at the same time intervals as hematologic endpoints. At sacrifice, relative organ weights were calculated for heart, spleen, kidney, liver, and testes. Histopathology was conducted on all animals for the following tissues: heart, lung, liver, kidney, urinary bladder, spleen, gastroenteric (organs not specified), skeletal muscle, bone marrow, skin, brain, thyroid, adrenal, pancreas, pituitary, and gonads.

With the exception of body weights (for which means at several time points were provided), no individual or summary data were given. No mortality occurred in any group (Borzelleca et al., 1964). Except for the initial emetic effects, no clinical signs of toxicity were observed. Slightly lower body weights occurred in high-dose dogs (up to 10% lower than controls; statistical analysis not reported), which were associated with a slight decrease in food consumption. Hematologic and urinary findings were within normal ranges. Relative organ weights in treated groups did not differ significantly from controls. Histopathologic evaluation did not show any treatment-related nonneoplastic or neoplastic effects. The NOAEL for this study was 22 mg/kg-day; a LOAEL could not be identified.

Reproductive/Developmental Studies

Pietrowicz et al. (1980)

One gavage developmental study was reported in a secondary review (Pietrowicz et al., 1980), as cited in European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 1994); the original study was published in a Polish journal and was not translated for this review. According to the review, pregnant Wistar rats (number not reported) were given daily gavage doses of 0, 25, 50, 100, 200, or 400 mg/kg-day of ethyl acrylate (purity and vehicle not specified) on Gestation Days (GDs) 7−16. Dams showed a decrease in body-weight gain and in placental weight. Fetal effects consisted of delayed ossification, shortened ribs, and skull anomalies; however, the review indicated that the effects were not dose related. No other information was provided in the review, including the dose levels at which the reported effects occurred. The review authors stated that flaws in the study design precluded comprehensive evaluation of the results. There was not enough information to identify effect levels for this study.

Inhalation Exposure

Miller et al. (1985)

Miller et al. (1985; Dow Chemical Co, 1983) conducted chronic-duration inhalation studies of ethyl acrylate in rats and mice. F344 rats (115/sex/exposure group and 92/sex for each of two control groups) were exposed to vaporized ethyl acrylate (>99.5% purity) at target concentrations of 0, 25, 75, or 225 ppm (0, 102, 307, or 921 mg/m^3) for 6 hours/day, for 5 days/week, for 27 months. Subgroups (10−20/sex/dose group) were sacrificed following 3, 6,

12, and 18 months of exposure. The highest exposure was discontinued after 6 months due to significantly reduced body-weight gain, and animals were held without further exposure for another 21 months. At the time of discontinuation of the highest exposure, another study was initiated using an exposure concentration of 5 ppm (21 mg/m^3) (90/sex/treated group and 80/sex/control group) and the same exposure regimen as the first study. Subgroups of animals were sacrificed at 6, 12, and 18 months following commencement of treatment (10−20/sex/dose group), and final sacrifice was at 24 months. Animals were observed daily for mortality and clinical signs of toxicity. In the first study, body weights were recorded prior to initiation of exposure, weekly for the first 3 months and biweekly for Months 4−6. In the 21-mg/m^3 study, body weights were recorded prior to initiation of exposure and monthly thereafter. At the 6-month interim sacrifice, hematology (total erythrocyte counts, hemoglobin, total and differential leukocyte counts) and clinical chemistry (alkaline phosphatase, serum glutamic pyruvic transaminase [alanine aminotransferase], blood urea nitrogen, glucose, cholesterol, fasting protein, triglycerides, total protein, albumin, and globulins) were analyzed. Evaluated end points for urinalysis were urobilinogen, bilirubin, glucose, ketones, blood, pH, protein, and specific gravity. At the 6-month interim sacrifice, liver, kidney, and brain were removed and weighed.

Pathology and histopathology were conducted at 3 and 6 months (Miller et al., 1985; Dow Chemical Co, 1983). The following tissues were examined grossly: liver, heart, pancreas, spleen, brain, pituitary, vertebrae (bone and bone marrow) with spinal cord, sciatic nerve, adrenals, kidney, stomach, small intestine, cecum, large intestine, rectum, mediastinal and mesenteric lymph nodes, urinary bladder, testes, epididymides, seminal vesicle, coagulating gland, prostate, ovaries, oviduct, uterus, cervix, lung, skeletal muscle, salivary gland, mediastinal tissue, aorta, esophagus, thyroid, parathyroid, trachea, skin (including subcutaneous tissue and mammary tissue when present), eyes, tongue, nasal turbinates, head, lacrimal glands, larynx, Zymbal gland, mesenteric tissue, and any other grossly recognized lesions. Animals that died during the study or were sacrificed in extremis were also necropsied. All tissues listed above were examined microscopically in the 0- and 307-mg/m^3 groups with the exception of male mammary tissue and the rectum. Histopathology of animals in the 102- and 921-mg/m^3 groups was more limited but included evaluation of liver, kidneys, lungs, nasal turbinates, testis, brain, heart, spleen, pancreas, adrenals, pituitary, thyroid/parathyroid, mediastinal and mesenteric lymph nodes, and all grossly recognized lesions suggestive of tumor formation. In the 5-ppm study, histological examination was limited to the target tissues (nasal turbinates). Nasal cavities were processed and examined at four cross-sectional levels. Nonneoplastic lesions in the olfactory tract were graded, based on severity and extent of distribution within the naval cavity.

Exposure-related mortality did not occur in any dosed rat group relative to controls throughout the studies (Miller et al., 1985; Dow Chemical Co, 1983). No clinical signs of toxicity were observed at 21, 102, or 307 mg/m^3. At 921 mg/m^3, rats appeared to be irritated and aggressive at the start of the daily 6-hour dosing period and lethargic at the end. Body-weight gains in males and females were lower than controls throughout the chronic-duration study at 307 and 921 mg/m^3 (data presented graphically). Based on visual inspection of the graphs, body-weight gains were in the range of 10−20% less than controls. Slight decreases were observed at 21 and 102 mg/m^3, but these were of a lesser magnitude (<10% of control values). Because body-weight data were only presented graphically as body-weight gain and no quantitative measure of the absolute body weights was available, the significance of the decreases in body-weight gain is unclear. No effects on hematology, clinical chemistry, or

urinalysis were noted. Absolute organ weights (organs were not specified) were statistically decreased only in the 921-mg/m^3 group (data not shown by study author), which the study authors attributed to the significant decrease in body-weight gain. At the 3- and 6-month interim sacrifices, histopathology was only observed in the olfactory tract in animals exposed to concentrations ≥102 mg/m^3 as compared with controls (incidence not given). Primary findings were reported as degeneration, necrosis, and hyperplasia of the olfactory epithelium, accompanied by an increase in glandular elements that were mostly ductal rather than secretory.

At terminal sacrifice, the only pathological and histopathological findings attributed to ethyl acrylate were in the nasal cavity of the rats (Miller et al., 1985; Dow Chemical Co, 1983). Treatment-related changes were present at exposure concentrations ≥102 mg/m^3 and increased in severity and extent of distribution with increasing concentrations. No qualitative or quantitative differences were observed between the sexes. Nonneoplastic histopathology is reported in Table 7. At 102 mg/m^3, nonneoplastic lesions were generally confined to the more anterior regions of the olfactory epithelium in the dorsal meatus and consisted of (1) a decrease in the number of mature neurons with compensatory hyperplasia and (2) stratification of the basal and reserve cells, accompanied by changes in glandular elements. In some animals, focal loss of olfactory epithelium was replaced by ciliated respiratory epithelium ("respiratory metaplasia"), generally occurring around the luminal openings of glandular elements. At 307 mg/m^3, histopathology was generally similar but was more extensive and included the ethmoid recess area in addition to the nasal cavity proper. In addition to basal cell hyperplasia, virtually all rats had areas of respiratory metaplasia, increased glandular elements, and focal mineralization of the olfactory epithelium. Affected areas in the ethmoid recess were limited to the dorsal and medial portions of the nasal cavity. Other nonneoplastic lesions in other organs and tissues were considered by the authors to be age related and not attributed to ethyl acrylate treatment. The authors noted that there were no appreciable changes in the extent and severity of lesions as the study progressed. No histopathological changes occurred in the nasal cavities at 21 mg/m^3. Based on histopathology in the olfactory tract, the NOAEL and LOAEL values for rats were 21 and 102 mg/m^3, respectively.

No treatment-related neoplasms occurred in rats at any concentration.

Table 7. Nonneoplastic Histopathological Changes in the Olfactory Epithelium of F344 Rats Exposed to Ethyl Acrylate Vapors for up to 27 Months

Observation	Exposure Concentrations in ppm (mg/m^3)[a]											
	Males						Females					
	Control A[b] (air)	Control B[b] (air)	Control C[c] (air)	5 (21)	25 (102)	75 (307)	Control A[b] (air)	Control B[b] (air)	Control C[c] (air)	5 (21)	25 (102)	75 (307)
Basal cell hyperplasia												
Slight	2[d]	0	0	0	68	1	0	0	0	0	55	4
Moderate	0	0	0	0	9	99	0	0	0	0	16	96
Increased intraepithelial glands												
Slight	0	0	0	0	42	1	0	0	0	0	12	0
Moderate	0	0	0	0	7	97	0	2	0	0	17	100
Respiratory metaplasia												
Slight	0	2	4	2	13	12	0	3	0	0	4	56
Moderate	2	2	0	0	3	83	0	0	0	0	2	24
Diffuse atrophy	2	2	0	0	5	0	0	1	0	0	0	0
Multifocal mineralization	0	0	0	0	1	87	0	0	0	0	8	87

[a]Results for the 225-ppm group are not shown because exposure of this group was stopped at 6 mo.
[b]These two control groups were run concurrently with the 25- and 75-ppm groups.
[c]This additional control group was run concurrently with the 5-ppm group (started 6 mo after the other groups).
[d]Numbers are cumulative percentages of animals with observed effects over the course of the study.

Source: Miller et al. (1985) and Dow Chemical Co (1983).

$B6C3F_1$ mice (105/sex/exposure group and 84/sex in each of two control groups) were exposed at the same concentrations, using the same exposure regimen and statistical methodology as those for rats (Miller et al., 1985; Dow Chemical Co, 1983). This includes the running of a second study with mice exposed to 21 mg/m^3. However, interim sacrifices (10−20/sex/group) were only conducted at 6, 12, and 18 months; clinical chemistry end points evaluated were limited to alkaline phosphatase, serum glutamic pyruvic transaminase, blood urea nitrogen, and glucose; urinalysis was not conducted; and the gall bladder was added as a target organ for gross pathology and histopathology. No treatment-related mortality occurred. As with rats, body-weight gains were significantly reduced relative to controls throughout the study at 307 mg/m^3. At 102 mg/m^3, a slight depression of body-weight gain occurred in both sexes, particularly during the latter part of the chronic-duration study. No hematologic, clinical chemistry, or significant organ-weight changes were reported at any dose level.

At the 6-month interim sacrifice, the only treatment-related histopathology occurred in the olfactory tract of mice at exposure concentrations ≥102 mg/m^3 (Miller et al., 1985; Dow Chemical Co, 1983, 1978). These findings were concentration related and were similar quantitatively and qualitatively in both sexes. The extent and severity of the histopathology increased with increasing exposure concentration. The primary effects were (1) degeneration, necrosis, and inflammation in the nasal turbinates and metaplasia of the olfactory epithelium, characterized as moderate in severity, at 921 mg/m^3; (2) degeneration, necrosis, and inflammation in the nasal turbinates, but no metaplasia, characterized as slight in severity, at 307 mg/m^3; and (3) focal degeneration and inflammation of the olfactory epithelium, characterized as very slight, at 102 mg/m^3. In each exposure group, all animals (5/5 in the 102- and 307-mg/m^3 groups, and 10/10 in the 921-mg/m^3 group) were affected. No histopathology was observed in the 21-mg/m^3 dose group or in the control group.

Nonneoplastic lesions observed at terminal sacrifice of mice are reported in Table 8. The most notable change at exposures ≥102 mg/m^3 was respiratory metaplasia, generally occurring in 5−25% of the olfactory epithelium, accompanied by the proliferation of ductal glandular elements in the submucosa beneath the altered epithelium (Miller et al., 1985; Dow Chemical Co, 1983). These glandular elements were generally dilated and frequently contained purulent exudate. A diffuse, mild inflammatory infiltrate was associated with submucosal effects in many animals. Lesions consisted of replacement of neuroepithelium with accompanying submucosal glandular proliferation in the nasal cavity and ethmoid recess. At 307 mg/m^3, lesions were similar but more extensive; at least 25−50% of the olfactory epithelium was replaced with ciliated respiratory epithelium, accompanied by hyperplasia in the underlying submucosal glands. Approximately 28−47% of mice in the control groups had identical morphological changes occurring in a much more limited distribution (affecting ≤5% of the olfactory mucosa), suggesting that these types of changes also occur spontaneously. No other gross or morphological changes occurred in any other tissue or organ. The study authors noted that the nature and extent of observed olfactory lesions were not dependent on exposure duration and did not increase appreciably throughout the course of the study. Exposure to 21 mg/m^3 of ethyl acrylate did not induce pathological or histopathological changes in the olfactory epithelium. Based on histopathology in the olfactory tract, the NOAEL and LOAEL values for mice were 21 and 102 mg/m^3, respectively.

Table 8. Nonneoplastic Histopathological Changes in the Olfactory Epithelium of B6C3F$_1$ Mice Exposed to Ethyl Acrylate Vapors for up to 27 Months

Observation	Exposure concentrations in ppm (mg/m^3)[a]											
	Males						Females					
	Control A[b] (air)	Control B[b] (air)	Control C[c] (air)	5 (21)	25 (102)	75 (307)	Control A[b] (air)	Control B[b] (air)	Control C[c] (air)	5 (21)	25 (102)	75 (307)
Hyperplasia of submucosal glands												
Very slight (focal, 0−5%)[d]	42[e]	26	8	7	4	1	28	39	20	24	3	0
Slight (5−25%)	0	2	0	0	48	1	0	2	0	0	81	0
Moderate (25−50%)	0	0	0	0	41	34	0	0	0	0	3	83
Severe (>50%)	0	0	0	0	0	61	0	0	0	0	0	14
Respiratory metaplasia of olfactory epithelium												
Very slight (focal, 0−5%)	47	30	6	2	0	1	28	39	14	15	3	0
Slight (5−25%)	0	3	0	0	56	1	0	2	0	2	81	0
Moderate (25−50%)	0	2	0	0	41	36	0	0	2	0	3	83
Severe (>50%)	0	0	0	0	0	61	0	0	0	0	0	14

[a]Results for the 225-ppm group are not shown because exposure of this group was stopped at 6 mo.
[b]These two control groups were run concurrently with the 25- and 75-ppm groups.
[c]This additional control group was run concurrently with the 5-ppm group (started 6 mo after the other groups).
[d]Values in parentheses indicate the relative portion of olfactory epithelium with alteration.
[e]Numbers are cumulative percentages of animals with observed effects over the course of the study.

Source: (Miller et al. (1985); Dow Chemical Co (1983)).

No treatment-related neoplasms occurred in mice at any concentration.

Reproductive/Developmental Studies

Murray et al. (1981)

Pregnant Sprague-Dawley rats (33 bred rats and 29−32 pregnancies per group) were exposed to ethyl acrylate (99.7% purity) for 6 hours/day on GDs 6−15 at inhalation concentrations of 0 (filtered air), 50, or 150 ppm (0, 205, or 614 mg/m^3) (Murray et al., 1981). Food and water were provided ad libitum but not during exposures. Maternal body weights were recorded on GDs 6, 8, 10, 12, 16, 18, and 21. Food and water consumption were recorded at 3-day intervals beginning on GD 6. The uterus was removed and weighed prior to sacrifice of dams on GD 21. Maternal livers were weighed. The number of corpora lutea and the number and position of dead, live, and resorbed fetuses were recorded. Uteri with no visible implantation sites were stained with ammonium sulfide (10%) to detect very early resorptions. After being weighed, measured (crown to rump length), and sexed, all fetuses were examined for external malformations. One-third of the fetuses per litter were examined by dissection for soft-tissue alterations. All of the fetuses from each litter were placed in 95% ethanol, stained with alizarin red S, and examined for skeletal anomalies.

No mortality occurred, and no signs of maternal clinical toxicity were evident (Murray et al., 1981). At 614 mg/m^3, maternal body weights on GDs 8, 10, 12, 16, and 18 were significantly ($p < 0.05$) decreased relative to concurrent controls. Body-weight gain was also significantly ($p < 0.05$) decreased on GDs 6−7 (loss of 16 g), and 12−15 (6 g lower weight gain than controls). Following termination of exposure on GD 15, dams in both treated groups gained significantly more weight than controls; at sacrifice, the total weight gain from GDs 6 to 20 was still significantly decreased at 614 mg/m^3. At 614 mg/m^3, food consumption was significantly reduced during GDs 6−14, which may account for the decreased weight gain seen at this dose. However, drinking water consumption (measured for 3-day intervals) was statistically elevated during GDs 6−20. At 205 mg/m^3, drinking water consumption was significantly increased on GDs 12−14, and food consumption was comparable to controls. No treatment-related changes in maternal liver weights occurred. No significant effects were observed on incidence of pregnancy, mean litter size, number of resorptions, fetal sex ratio, or fetal crown-to-rump lengths. Mean fetal body weight was similar to controls in the 205-mg/m^3 group but was significantly *increased* in the 614-mg/m^3 group; this finding was not considered by the study authors to be toxicologically significant. At 614 mg/m^3, three fetuses from 3 different litters (out of a total of 29 litters) had hypoplastic tails; one of these fetuses also had missing vertebrae, another had a small anal opening and missing vertebrae, and the third had missing vertebrae and centra, a small anal opening, a short trunk, ectopic ovaries, and fused ribs. Compared to concurrent controls (32 litters), these findings were not statistically significant; however, statistical analyses are often of little use in the analysis of rare-event malformations. Very similar malformations occurred in fetuses from three different 614 mg/m^3 litters and no control litters, and one of these malformations (hypoplastic tail) was also above historical control levels for the lab (~1% occurrence out of 800 litters compared to ~10% in the current study). A significant *decrease* in the number of fetuses with delayed ossification was observed at 205 mg/m^3 (cervical centra) and 614 mg/m^3 (cervical centra, sternebrae). These findings were considered to be normal variations and not toxicologically significant. Based on reduced maternal body-weight gain during gestation, the maternal NOAEL and LOAEL values were 205 and 614 mg/m^3, respectively. Based on fetal malformations, the NOAEL for developmental toxicity is also 205 mg/m^3, and the LOAEL is 614 mg/m^3.

Saillenfait et al. (1999)

Pregnant Sprague-Dawley rats (20 bred rats and 17−19 pregnancies per group) were exposed to ethyl acrylate (>99% purity) for 6 hours/day on GDs 6−20 at airborne concentrations of 0 (filtered air), 25, 50, 100, or 200 ppm (0, 102, 205, 409, or 820 mg/m^3) (Saillenfait et al., 1999). Food and water were provided ad libitum but not during exposures. Maternal body weights were recorded on GDs 0, 6, 13, and 21. Food consumption was measured for the intervals GDs 6−13 and 13−21. Following euthanasia of dams on GD 21, the uterus was removed and weighed. The numbers of implantation sites, resorptions, and dead and live fetuses were recorded. Uteri with no visible implantation sites were stained with ammonium sulfide (10%) to detect very early resorptions. Live fetuses were weighed, sexed, and examined for external anomalies, including those of the oral cavity. Half of the live fetuses from each litter were preserved in Bouin's solution and examined for internal soft-tissue changes. The other half were fixed in 70% ethanol, eviscerated, and examined for skeletal abnormalities following staining with alizarin red S. The litter was used as the basis for analysis of fetal variables.

No mortality was observed during the study (Saillenfait et al., 1999). Clinical signs of toxicity during treatment were not reported. In the 821-mg/m^3 group, maternal body-weight gain throughout the exposure and absolute weight gain (corrected for uterine weight) were significantly reduced (25−50% lower weight gain than controls at various intervals, and net loss of 17 g absolute weight; $p < 0.05$ for both). No data on food consumption were available because of a technical failure. No reproductive or developmental effects were observed for any measured end point with the exception of fetal body weights in both sexes (7−8% lower than controls; $p < 0.01$) in the 820-mg/m^3 group. Single occurrences of visceral malformations were observed in all groups, including controls. The incidences of external, visceral, and skeletal variations were scattered among groups, with no evidence of a relationship with treatment. Based on these findings, the maternal NOAEL and LOAEL values were 409 and 820 mg/m^3, respectively, based on reduced body-weight gain. The developmental NOAEL and LOAEL values are also 409 and 820 mg/m^3, respectively, based on reduced fetal body weight.

OTHER STUDIES

Toxicokinetics

Absorption of ethyl acrylate from the gastrointestinal tract and respiratory tract is extensive and rapid. Ghanayem et al. (1987) reported that >90% of radiolabeled ethyl acrylate at single doses of 100, 200, or 400 mg/kg, administered by gavage in corn oil vehicle to F344 rats was absorbed within 4 hours, with negligible amounts of radioactivity being detected in the stomach contents at 24 hours postdosing. Tissue distribution analysis at 4 hours following dosing demonstrated that the highest concentrations of radioactivity were found in the forestomach, glandular stomach, intestine, liver, and kidneys. Fractionation of the forestomach and liver showed that in the forestomach, the highest amount of radioactivity was associated with the protein fraction, whereas in the liver, the highest percentage of radioactivity was associated with the lipid fraction. At 24 hours postdosing, the majority of radioactivity had been cleared, although some radioactivity was still associated with the protein fraction in the forestomach. No binding to nucleic acids could be detected (limit of detection = 1 alkylation per 10^4 nucleotides). The study authors concluded that ethyl acrylate is rapidly metabolized to C_1 and C_2 fractions, which freely enter the normal synthetic pathways of the cell, and that direct alkylation does not occur.

During a 2-hour "nose-only" inhalation exposure to 225-ppm ethyl acrylate vapor, absorption in rats reached an apparent plateau within 10−20 minutes and subsequently remained relatively constant; approximately 60% of the administered dose was absorbed in the upper respiratory tract by the end of the study (Stott and McKenna, 1984).

Metabolism of ethyl acrylate occurs via two basic pathways: hydrolysis and conjugation (de Bethizy et al., 1987; NTP, 1986). Following in vitro or in vivo dosing, the ester bond is rapidly hydrolyzed by carboxylesterase enzymes, generating ethanol and acrylic acid (Ghanayem et al., 1986). Acrylic acid is subsequently metabolized oxidatively to acetyl coenzyme A via the propionic acid pathway.

Following inhalation exposure, ethyl acrylate is rapidly hydrolyzed in the upper respiratory tract, with the highest V_{max} being observed in the olfactory epithelium (3-fold greater than in the respiratory epithelium). The hydrolytic half-life of ethyl acrylate ranged from 0.06 seconds for olfactory epithelium to 0.23 seconds for respiratory epithelium (Frederick et al., 1994). Stott and McKenna (1984) estimated that approximately 50% of ethyl acrylate passing through the upper respiratory tract will be hydrolyzed in situ by carboxylesterases.

Conjugation of the ethenyl group (CH_2−CH−) with the sulfhydryl group of GSH and subsequent urinary excretion of mercapturic acid derivatives is another pathway of ethyl acrylate metabolism. The reaction with GSH can occur either enzymatically via GSH transferases or directly through a Michael addition reaction (ECETOC, 1994). Ethyl acrylate binds with glutathione in vitro and has been shown to decrease tissue nonprotein sulfhydryl following in vivo inhalation exposure (Silver and Murphy, 1981).

In vitro studies of ethyl acrylate in a range of tissues have shown that metabolism of ethyl acrylate occurs in the forestomach, glandular stomach, stomach contents, and blood of male and female F344 rats (NTP, 1986, Appendix M). Metabolism followed first-order kinetics and occurred most rapidly in blood, with no significant sex differences. Estimates of half-lives were 14 or 12 (male, female) minutes in blood, 53 and 73 (male, female) minutes in stomach contents, 67 and 66 (male, female) minutes in glandular stomach tissue, and 76 and 96 (male, female) minutes in forestomach tissue. Following in vivo gavage administration of doses up to 200 mg/kg-day (NTP, 1986, Appendix M), any systemically absorbed ethyl acrylate was shown to rapidly hydrolyze in the blood and/or liver and not to circulate throughout the body. Consequently, the only tissue receiving significant exposure to ethyl acrylate was the forestomach.

Following single gavage dosing of rats with radiolabeled ethyl acrylate at 2, 20, or 200 mg/kg, the dosed radioactivity was rapidly excreted, with 60 and 75% of administered dose eliminated at 8 and 24 hours, respectively (de Bethizy et al., 1987). The primary excretory metabolite was CO_2, accounting for 52−61% of administered radiolabel. Urinary and fecal excretion accounted for 8−28 and 2−6% of dosed radioactivity, respectively. High performance liquid chromatography analysis of urine showed the presence of 3-hydroxyproprionic acid and two metabolites derived from glutathione conjugation, *N*-acetyl-*S*(carboxymethyl)cysteine and *N*-acetyl-*S*(carboxymethyl)cysteine ethyl ester. The excretion of the *N*-acetyl cysteine derivatives, expressed as a percentage of the administered dose, decreased in a dose-dependent manner, which was attributed by the study authors to glutathione depletion. Derivatives of glutathione conjugates of ethyl acrylate and acrylic acid in the urine of rats following gavage

dosing were also observed by Ghanayem et al. (1991c). No evidence was found in either study for the presence of epoxidation products, 2,3-epoxypropionic acid, *N*-acetyl-*S*(2-carboxy-2-hydroxyethyl)cysteine and its ethyl ether, in either in vivo or in vitro studies. The study authors concluded that epoxidation of the ethenyl group of ethyl acrylate during metabolic transformation is unlikely.

Silver and Murphy (1981) examined the effect of the carboxylesterase inhibitor triorthotolyl phosphate (TOTP) on metabolism and nonprotein sulfhydryl (NPSH) depletion in selected tissues following a 4-hour inhalation exposure of ethyl acrylate (98.5% purity) by male Holtzman rats. Plasma and lung, liver, and kidney tissue homogenates were analyzed in vitro following termination of exposure to assay tissue-specific carboxylesterase metabolism. Esterase activity was highest in the liver, followed by the lung (which showed one-fourth of the activity of the liver) and the kidney. Plasma hydrolytic activity was low. No significant changes occurred in NPSH tissue homogenates following inhalation exposure. Pretreatment of rats with various doses of TOTP prior to sacrifice resulted in a significant inhibition in esterase activity in all tissue homogenates examined; inhibition increased with increasing TOTP dose. TOTP pretreatment also significantly reduced NPSH levels in liver, lung, kidney, and plasma, as compared with corn oil vehicle, with the largest effects occurring in the lung. The study authors suggest that hydrolysis of ethyl acrylate following inhalation exposure may be a more significant detoxification pathway than glutathione conjugation in the examined tissues.

Acute or Short-term Studies

Sprague-Dawley rats (15/sex/dose group) were given ethyl acrylate (purity not specified) dissolved in corn oil (2%) by gavage at a daily dose of 200 mg/kg-day for 28 days (FDRL, 1986). Five animals/sex/group were sacrificed at exposure termination; the remaining animals were maintained untreated for either 3 or 6 additional weeks (5/sex/dose group at each time period) to evaluate the potential reversibility of effects. Animals were observed daily for mortality and clinical signs of toxicity. Body weight, weight gain, and food consumption were determined weekly. All animals were given a complete gross necropsy. The forestomach and glandular stomach were weighed and examined for gross abnormalities and histopathology. Mortality was not observed. The only statistically significant clinical observation was an increase in salivation in males (29% in treated groups versus 0% in controls) on Study Day 26. Although food consumption was significantly decreased in both sexes during the study, body weight and body-weight gain were unchanged. Both sexes showed a statistically significant increase in absolute and relative weight of the forestomach; there was an increase in the absolute but not relative glandular stomach weight in females only. In pathological examination, no gross nodules were observed. However, the forestomach in treated animals was characterized by a diffuse thickening of the mucosa in all animals of both sexes at study termination, which was still present in 2/5 males sacrificed after the 3-week recovery period and in 3/4 males sacrificed at 6 weeks following treatment termination. Microscopic examination at the end of the dosing period showed statistically significant increases in the incidences of mild-to-moderate multifocal papillomatous and nodular hyperplasia and mild-to-moderate diffuse epithelial hyperplasia, hypertrophy of the lamina propria, and hyperkeratosis. Histopathology was still evident in animals after 3 or 6 weeks of recovery, but the severity was decreased. No changes were observed in the glandular stomach.

Frederick et al. (1990) dosed male F344 rats with ethyl acrylate (≥99% purity) either by daily gavage or in the drinking water for 2 weeks. Gavage (14 rats/treatment group) doses were 0, 2, 10, 20, 50, 100, and 200 mg/kg-day, and drinking water (20 rats/treatment group) concentrations were 0, 200, 1,000, 2,000, and 4,000 ppm (corresponding to 0, 23, 99, 197, and 369 mg/kg-day, respectively, as calculated by study authors). In animals dosed by gavage, irritation and lesions of the forestomach increased in incidence and severity over the 20-200 mg/kg-day-dose range. At corresponding drinking water dose levels, a much lower incidence of forestomach irritation and less severe lesions were observed. No lesions were observed in the glandular stomach via either dose route.

In 14-day range-finding studies conducted to identify appropriate dose levels for 13-week and 2-year studies (NTP, 1986), no toxic effects were observed at gavage doses in corn oil vehicle up to 200 mg/kg-day and in drinking water at concentrations up to 0.45 and 0.22% in rats and mice, respectively. Therefore, additional studies were conducted at higher doses. F344 rats and $B6C3F_1$ mice (5/sex/group) received ethyl acrylate (≥99% purity) at doses of 0, 100, 200, 400, 600, or 800 mg/kg in corn oil vehicle by gavage for 14 consecutive days. A thickened stomach wall and abdominal adhesions were observed in 1/5 male rats and 3/5 females at 100 mg/kg-day, 4/5 males and 4/5 females at 200 mg/kg-day, 4/5 males and 5/5 females at 600 mg/kg-day, and all animals of both sexes at 400 and 800 mg/kg-day. Histologically, ulcer-like and nonulcerative inflammation of the forestomach was observed at 400 mg/kg-day (5/5 males and 4/5 females). No inflammatory reactions or lesions were observed at lower doses.

In mice, the forestomach was grossly thickened in all males at doses ≥200 mg/kg-day, in l/5 males at 100 mg/kg-day, in all females at ≥400 mg/kg-day, and in 1/5 females at 200 mg/kg-day (NTP, 1986). Histologically, ulcerative inflammation in the forestomach was found in 4/4 males and 5/5 females at 600 mg/kg-day (800 mg/kg-day group not examined) and in 1/5 males at 400 mg/kg-day. No lesions of toxicological significance were found in mice of either sex at doses <200 mg/kg-day.

A series of short-term studies were conducted to investigate the relationship between dose, route, histopathology of the forestomach and glandular stomach, and recovery following cessation of dosing (Ghanayem et al., 1986, 1985a, b). In the first study, F344 male rats administered a single dose of ethyl acrylate (≥99% purity) in corn oil via gavage at 0 (15 rats), 100 (8 rats), 200 (8 rats), or 400 mg/kg (8 rats) (dose volume standardized to 5 mL/g) (group sizes estimated based on the number of animals reported in data tables) developed mucosal and submucosal edema and vacuolization of the tunica muscularis in the forestomach and mild submucosal edema of the glandular stomach (Ghanayem et al., 1985b). Equivalent subcutaneous or intraperitoneal dosing did not produce any toxicologically significant gastric lesions. Gavage administration of rats with two or four consecutive oral daily doses at 200 mg/kg-day caused mucosal edema associated with vesicle formation, mucosal hyperplasia, submucosal edema and inflammation, vacuolization of the tunica muscularis, and mucosal erosions or ulcers in the forestomach. Submucosal edema, inflammation, and mucosal erosions or ulcers were also reported in the glandular stomach following repeated gavage dosing. The study authors suggested that gastric lesions may result from localized hemodynamic changes following oral bolus dosing and were characteristic of a classical, immediate inflammatory response to an injurious agent at the site of administration.

In a second study, ethyl acrylate (99% purity), at a single gavage dose of 2 mmol/kg (400 mg/kg) to 8 male F344 rats (group sizes estimated based on the number of animals reported in data tables), caused intercellular and intracellular mucosal edema and submucosal edema in the forestomach (Ghanayem et al., 1985a). An estimated 15 rats (estimated from data tables) were administered corn oil via gavage as a control. In the glandular stomach, a low incidence of mucosal congestion and a high incidence of submucosal edema were observed. A maximum response was reached 8 hours following ethyl acrylate administration. The forestomach edema increased markedly when the dose was doubled to 4 mmol/kg (800 mg/kg). Decreasing the volume of the corn oil vehicle at a 2-mmol/kg (400 mg/kg) dose increased the incidence of gastric edema, suggesting a dose-concentration effect. This finding was more pronounced in the forestomach than the glandular stomach. Administration of ethyl acrylate in a water mixture (water-Emulphor) significantly increased the incidence of gastric edema, suggesting that lipid solubility of the vehicle affected stomach absorption and, consequently, gastric toxicity by altering the delivery of dose to the tissue. Corn oil is not as well absorbed as water by stomach tissue, and thus, the administered dose tends to remain in stomach contents rather than enter stomach tissue. Comparison of ethyl-acrylate-induced findings with those for equimolar concentrations of the methyl or ethyl esters of methacrylic acid (methyl and ethyl methacrylates, respectively) and for structural-saturated analogs of methyl or ethyl acrylates (methyl and ethyl propionate, respectively), tested under identical conditions, did not cause gastric toxicity in either the forestomach or glandular stomach. The study authors concluded that structural requirements for acrylate esters to cause gastric toxicity include a complete ester linkage, an unsubstituted double-bond between Carbons 1 and 2 of the acrylic moiety, and no substitution at Carbon 2.

In the third study, F344 male rats were given 14 daily gavage doses of 0 (24 rats), 100 (28 rats), or 200 mg/kg (28 rats) ethyl acrylate (≥99% purity) in corn oil (Ghanayem et al., 1986). The 100-mg/kg-day group was sacrificed at 1, 7, or 14 days following the last dose; the 200-mg/kg-day group was sacrificed at 1, 14, or 28 days following the last dose. A significant decrease in body-weight gain occurred during the 2 weeks of treatment in the high-dose group; however, body weights after the last of the daily doses were comparable to those in the low-dose and vehicle controls. No histopathology was observed in the glandular stomach after 14 days of treatment. This finding differs from those in the acute studies, in which microscopic changes were observed in the glandular stomach after 1−4 days of gavage dosing and suggests glandular stomach adaptation to ethyl acrylate administration with repeated dosing for more than 4 days. However, forestomach lesions were still present and were most pronounced in the high-dose group. At 100 mg/kg-day, forestomachs were slightly thickened, whereas rats treated with 200 mg/kg-day exhibited severe papillomatous thickening and entrapment of hair shafts and feed particles in the forestomach mucosa. Histopathological lesions included marked generalized hyperkeratosis and moderate-to-marked generalized hyperplasia of the stratified squamous cell mucosal layer. Additional lesions were observed at 200 mg/kg-day, including multiple mucosal ulcers, accompanied by purulent inflammation in adjacent mucosal epithelium, and severe submucosal inflammation in the vicinity of mucosal ulcers. The submucosal inflammation was characterized by infiltration of neutrophils and leucocytes and onset of fibrosis. All intact mucosal surfaces showed hyperplasia and hyperkeratosis.

At sacrifice (14 days following cessation of dosing), complete recovery had occurred in the forestomach of rats treated with 100 mg/kg-day, whereas the forestomach of rats treated with 200 mg/kg-day still exhibited numerous lesions (Ghanayem et al., 1986). After 4 weeks of recovery, mucosal hyperplasia was still observed in the high-dose group. Further, two novel

lesions, submucosal fibrosis and foreign body reaction, increased during the recovery period; these appear to have resulted from entrapment of hair and/or feeding particles in the lesions during the course of healing.

Other Routes

No skin tumors were observed in transgenic Tg.AC mice given dermal applications of ethyl acrylate 3 times/week for 20 weeks (Tennant et al., 1996). This transgenic mouse strain was created by the germline insertion of a mutated v-Ha Ras under the regulation of a fetal zeta-globin promoter. Animals of this genotype exhibit characteristics of genetically initiated skin and, thus, have a much shorter latency period to skin tumor formation following topical application of a chemical agent than normal mouse strains. Significant skin irritation occurred at the site of dermal contact.

Mechanistic Studies

Several mechanistic studies have been conducted to assess the mode of action of ethyl-acrylate-induced lesions and tumors in the forestomach following gavage, and to a lesser extent, of lesions in the olfactory tract following inhalation exposure. These studies have focused on changes in nonprotein sulfhydryls (glutathione substrate) and carboxylesterases (enzymes) involved in the metabolism and detoxification of ethyl acrylate and cell proliferation.

NPSH Reduction/Depletion

Following a single gavage dose to F344 rats of either 100- or 200-mg/kg ethyl acrylate, concentrations of NPSH were significantly reduced in both the forestomach and glandular stomach (NTP, 1986, Appendix M). However, the time-course and extent of depletion of NPSH varied significantly between the two target organs. At 30 and 120 minutes following dosing with 100 mg/kg, NPSH levels were approximately 30 and 16% of controls, respectively, in the forestomach. At 200 mg/kg, NPSH levels were 17 and 14% of control values, at 30 and 120 minutes, respectively, after dosing. In the glandular stomach, NPSH was reduced to approximately 50% of controls at 30 minutes after dosing with 100 mg/kg, and no further decreases were observed at the 120-minute time point. At 200 mg/kg, NPSH was approximately 40% of controls at 30 minutes and did not significantly decrease further at 120 minutes. Thus, the magnitude of NPSH depletion in the glandular stomach was less than that in the forestomach and did not show significant time-dependent changes following dosing. The study authors attribute the differences in NPSH depletion between the forestomach and stomach as being due to either the unique sensitivity of this organ to ethyl acrylate and/or the high concentration received by the forestomach following a gavage dose, as compared with the glandular stomach.

Frederick et al. (1990) measured the incidence and severity of forestomach and glandular stomach lesions in male F344 rats dosed by gavage or drinking water for 2 weeks at a range of doses (2−200 mg/kg-day) and determined the total NPSH content of the forestomach and glandular stomach and the NPSH concentrations in the liver 2−24 hours after the last gavage or drinking water dose. At a gavage dose of 200 mg/kg-day, total NPSH in the forestomach was rapidly depleted, reaching 11% of the initial value at 6 hours postdosing. The incidence and severity of forestomach histopathology increased at doses ≥20 mg/kg-day, with moderate-to-severe hyperplasia, accompanied by hyperkeratosis, submucosal inflammation, and ulceration/erosion occurring at 200 mg/kg-day. At 24 hours postdosing, NPSH content in the 200-mg/kg-day group was 4 times that of control animals (vehicle only), reflecting excess-induced NPSH synthesis or "compensatory overshoot." In contrast, equivalent drinking

water doses did not induce significant NPSH depletion; tissue concentrations were only slightly elevated, and lesions were of minimal-to-mild severity. In the glandular stomach, NPSH was slightly depleted at 6 hours postdosing by gavage at 200 mg/kg-day and increased less than 75% relative to control values at 24 hours postdosing. Drinking water exposures at approximately the same dose resulted in only a slight elevation of NPSH at this time period. No significant changes were observed in the liver at 2 weeks following dosing by either route. These observations suggest that bolus dosing of ethyl acrylate induced severe depletion of critical cellular thiols in the forestomach, with consequent toxic effects, but not in the glandular stomach or liver. Small changes in forestomach NPSH following drinking water exposures at a similar dose were considered to demonstrate adaptation and detoxification without inducing comparable forestomach toxicity at the same daily body burden.

Depletion of forestomach NPSH to 11−17% of control values, observed in the Frederick et al. (1990) and NTP (1986), Appendix M) studies, has been associated with severe cytotoxicity in other tissues in other studies (Clayson et al., 1990; Frederick et al., 1990).

Ghanayem et al. (1991a) examined the effects of treatment with sulfhydryl-depleting and sulfhydryl-containing agents on forestomach edema induced by ethyl acrylate gavage administration in F344 rats. Depletion of indigenous sulfhydryls by fasting or pretreatment with diethylmaleate reduced the extent and magnitude of ethyl acrylate-induced forestomach edema. In contrast, pretreatment of rats with sulfhydryl-containing chemicals such as cysteine or cysteamine potentiated forestomach edema. The study authors suggest that modulation of indigenous sulfhydryls plays a significant role in ethyl-acrylate-induced forestomach toxicity (Ghanayem et al., 1991a; de Bethizy et al., 1987)).

In studies by de Bethizy et al. (1987), Sprague-Dawley rats were administered single gavage doses of ethyl acrylate of 0 (corn oil vehicle), 2, 20, 100, or 200 mg/kg. At the highest dose, a significant increase in forestomach weight, accompanied by gross evidence of edema, was observed. Similar changes did not occur in the glandular stomach. An essentially linear depletion of NPSH content of the forestomach and glandular stomach was noted at 1 hour following dosing at the two lowest levels. However, at the two highest doses (100 and 200 mg/kg), the NPSH content did not change with dose, suggesting that the reactive thiols had been depleted. No dose-dependent changes in NPSH content were observed in the liver or the blood. Treatment with the carboxylesterase inhibitor, tri-o-cresyl phosphate (TOCP), 18 hours prior to ethyl acrylate dosing increased forestomach weight but did not significantly alter NPSH depletion in either the forestomach or the glandular stomach. However, pretreatment with TOCP did induce significant NPSH depletion in the liver. These findings suggest that the primary route of detoxification in the forestomach is via conjugation with glutathione, which is depleted at higher doses, resulting in in situ toxicity. In extragastric sites such as the liver, which is remote from the forestomach, ethyl acrylate hydrolysis by carboxylesterases is more extensive and rapid than glutathione conjugation. Inhalation exposure experiments by Silver and Murphy (1981) described above under ***Toxicokinetics***, also suggest that hydrolysis of ethyl acrylate predominates in the lung, liver, kidney, and blood; nasal turbinates were not examined in this study.

Increased Cell Proliferation

Ghanayem et al. (1991b) investigated the effects of gavage administration of 0, 50, 100, or 200 mg/kg-day of ethyl acrylate on cell proliferation in the forestomach and liver, using implanted osmotic minipumps containing bromodeoxyuridine (BrDU). In the forestomach, there was a dose- and time-dependent increase in epithelial cell proliferation, which correlated well with histopathological evaluation, primarily hyperplasia, at the higher doses. No increase in cell proliferation or histopathology was observed in the liver.

Gillette and Frederick (1993) assessed forestomach and glandular stomach cell proliferation in the F344 rat following single or multiple gavage doses of ethyl acrylate in corn oil vehicle. At a single gavage dose of 200 mg/kg, the number of S-phase nuclei *decreased* relative to concurrent control values immediately following gavage dosing, with the minimum level being achieved at 6 hours postdosing. However, by 20 hours postdosing, the number of S-phase nuclei had *increased* significantly above control values and remained elevated for at least 48 hours following administration of the single dose. This experiment was repeated with single doses of 0, 2, 10, 20, 50, 100, or 200 mg/kg. A significant dose-related increase in S-phase nuclei occurred at doses ≥20 mg/kg. In a subsequent repeated dose study, rats gavaged daily for 2 weeks at ethyl acrylate doses of 0, 10, 50, or 200 mg/kg-day showed prolonged elevation of S-phase nuclei only in the 200-mg/kg dose group during the 24 hours after the last dose. Increases in S-phase nuclei were not observed in lower dose groups, suggesting localized metabolic adaptation with repeated dosing at ≤50 mg/kg-day. In the glandular stomach, a transient increase in the S-phase response was observed only following a single 200-mg/kg dose relative to controls; in the repeated-dose study, a marginally significant increase in S-phase nuclei was observed only at 200 mg/kg-day at 18 hours postdosing. This increase was reported to be declining at 24 hours postdosing, the last time point measured in the study.

These cell proliferation findings were compared with the results of the study by Frederick et al. (1990), which measured NPSH depletion in the forestomach and glandular stomach using the same experimental protocol. The comparison suggested that cell proliferation and NPSH depletion are correlated and overlap temporally, with NPSH reduction preceding S-phase induction in both target organs and being larger in magnitude in the forestomach than the glandular stomach. This pattern of tissue changes has been reported for other forestomach carcinogens such as butyl hydroxyanisole (BHA) (Clayson et al., 1990).

Increased cell proliferation was also reported in rats during a 12-month treatment of ethyl acrylate at a dose (200 mg/kg-day) that also induced significant forestomach hyperplasia during the exposure period and led to the development of forestomach tumors during a subsequent recovery period of 2−9 months (Ghanayem et al., 1994). The study authors concluded that the time of sustained enhancement of cell proliferation plays a critical role in ethyl-acrylate-induced forestomach carcinogenicity, indirectly resulting in additional genetic damage and contributing to tumor development.

Genotoxicity

Ethyl acrylate has been extensively tested for mutagenicity and genotoxicity in both in vitro and in vivo test systems. In *Salmonella typhimurium* bacterial assays from a number of different laboratories, ethyl acrylate was negative in strains TA98, TA100, TA1535, TA1537,

and TA1538, with and without metabolic activation, in both the standard plate incorporation and liquid preincubation assays (Zeiger et al., 1992; Waegemaekers and Bensink, 1984; Rohm and Haas Co, 1980).

A modified *S. typhimurium* assay was conducted to assess the mutagenicity of ethyl acrylate and other similar compounds (Emmert et al., 2006). To compensate for lack of cytochrome P450 2E1 (CYP2E1) in conventional bacterial metabolizing systems, methyltranferase-deficient *S. typhimurium* strain YG7108 was transfected with plasmid pin3ERb_5. This plasmid contains DNA encoding for a complete electron transport chain, composed of P450 reductase, cytochrome b_5, and CYP2E1. Under the conditions of this assay, ethyl acrylate was negative.

In the Chinese hamster ovary (CHO) HGPRT mutation assay, ethyl acrylate was consistently negative in the absence of metabolic activation and was not tested in the presence of metabolic activation (Moore et al., 1988). Based on concerns that the CHO/HGPRT forward mutation assay does not identify compounds that induce base pair deletions (because the target gene is located on the X chromosome), an alternate in vitro study using the AS52/XPRT assay was performed (Newton et al., 1996). The target XPRT gene is stably integrated into an autosomal location and may have a higher sensitivity for detecting base-pair deletions. Ethyl acrylate was negative under the conditions of this test. In general, the XPRT test system showed good concordance with findings in the CHO/HGPRT assay.

In contrast, ethyl acrylate induced mutant colonies in the mouse lymphoma $TK^{+/-}$ mutation assay with L5178Y cells with and without metabolic activation (Dearfield et al., 1991; Moore et al., 1989, 1988). The majority of mutant colonies were reported to be small in size and occurred at cytotoxic concentrations with low cell survival rates, indicating that observed mutagenicity was the result of clastogenic activity (Dearfield et al., 1991; Moore et al., 1989, 1988). In clastogenic studies in vitro, ethyl acrylate induced chromosomal aberrations in the absence of S9 mix in L5178Y cells (Moore et al., 1988) and in Chinese hamster lung (CHL) and CHO cell lines with activation (Loveday et al., 1990; Ishidate et al., 1981). In isolated mouse splenocytes in vitro, ethyl acrylate had no effect on chromosomal aberrations or sister chromatid exchange (SCE) in cells tested during G_0 (resting phase) of the cell cycle, even at highly toxic concentrations (Kligerman et al., 1991). However, the chemical did induce chromosomal aberrations—but not SCE—when tested at near-toxic concentrations on splenocytes in late G_1/early S phase of the cycle. Ethyl acrylate produced a weak increase in SCE in CHO cells when tested with activation but not without (Loveday et al., 1990).

Ciaccio et al. (1998) investigated the mechanisms of ethyl-acrylate-induced cytotoxicity and mutation frequency in the in vitro mouse lymphoma assay by measuring (1) NPSH levels; (2) mitochondrial rhodamine 123 uptake; (3) DNA elution slope (single strand breakage) and Y intercept of fitted curves (cytotoxicity and double-strand breakage) in an alkaline elution assay; (4) cell death; and (5) pulsed-field gel electrophoretic resolution of high-molecular weight DNA. Ethyl acrylate reduced NPSH in both a time- and concentration-dependent manner, and marked reductions in mitochondrial rhodamine 123 uptake were observed following 4 hours of exposure at concentrations ≥10 µg/mL. No inductions of single-strand breaks occurred in the elution assay, and only highly cytotoxic concentrations (40−50 µg/mL) of ethyl acrylate (producing 80−87% reduction in cell numbers) caused increases in the elution slope and parallel drops (Y intercept) in the elution curve. At these cytotoxic concentrations, evidence for cell

death, cell necrosis, and DNA double-strand breaks occurred; these findings were considered to be secondary to severe cellular injury. The study authors concluded that ethyl-acrylate-induced mutagenic responses in the mouse lymphoma assay correlated best with cellular cytotoxicity mediated by NPSH depletion and mitochondrial membrane impairment (Ciaccio et al., 1998).

In a transformation assay using a cloned BALB/c-3T3 cell line, ethyl acrylate treatment induced severe cytotoxicity, but transformation rates were not significantly different from spontaneous rates for this cell line (Matthews et al., 1993).

Yang and Duerksen-Hughes (1998) investigated whether changes in p53 cell protein levels in the mouse fibroblast cell line NCTC 929 following chemical exposure could serve as an indicator for identifying potential DNA damage. The tumor suppressor gene p53 expresses a p53 binding protein that can act as a positive or negative modulator of transcription and also plays a key role in cell cycle control and prevention of uncontrolled cell proliferation. Ethyl acrylate increased cellular p53 levels only at plate concentrations that also induced cytotoxicity. The authors concluded that these findings are consistent with those of other studies demonstrating that cells respond to DNA damage induced by severe cytotoxicity by increasing their p53 protein levels, which prevents replication of damaged DNA during compensatory cell replication (Yang and Duerksen-Hughes, 1998).

In vivo studies are predominantly negative, with four of five mouse micronucleus tests showing that ethyl acrylate is inactive in the bone marrow (Ashby et al., 1989; Przybojewska et al., 1984). In the study by Przybojewska et al. (1984), statistically significant increases in the incidence of micronucleated polychromatic erythrocytes were observed in the bone marrow of Balb/c mice following two intraperitoneal doses (24 hours apart) and sacrifice at 6 hours following administration of the second dose. Doses ranged from 225 to 1,800 mg/kg (the highest dose approximating the LD_{50}). However, significant reductions in the ratio of polychromatic to normochromatic erythrocytes were observed at all dose levels, indicating that ethyl acrylate was cytotoxic in the bone marrow. Thus, positive findings occurred only at concentrations that induced severe cellular injury. These positive data could not be reproduced in four micronucleus tests in two species of mice (Balb/c and C57BL6) even when using test conditions that were identical to those of (Ashby et al., 1989; Przybojewska et al. (1984)). The reasons for this discrepancy are not known. However, cytotoxicity was noted to be statistically and biologically significant, as measured by the ratio of polychromatic to normochromatic erythrocytes (Ashby et al., 1989) in all five micronucleus studies. No significant increases in the incidence of chromosomal aberrations or SCEs were seen in splenocytes isolated from C57BL/6 mice at 24 hours following intraperitoneal injection with ethyl acrylate at doses ranging from 125 to 1,000 mg/kg (Kligerman et al., 1991). A small elevation in micronucleus formation in binucleated splenocytes was observed in one animal (out of five) in the highest dose group; however, the overall mean increase was less than 2-fold as compared with background and was not considered to be biologically significant (Kligerman et al., 1991).

Ethyl acrylate was negative in a sex-linked recessive lethal test with *Drosophilia melanogaster* following either oral or intraperitoneal dosing (Valencia et al., 1985).

No DNA adducts were observed in the forestomach (limit of detection = 1 alkylation/10^4 nucleotides) of rats treated by gavage with doses up to 400 mg/kg (Ghanayem et al., 1987). In a study published in Japanese and summarized in a secondary review (Morimoto et al., 1991), as

cited in ECETOC (1994), no DNA damage was induced, as detected by alkaline elution, in the forestomach squamous epithelium of rats administered a single gavage dose of 0.1−4% (5−200 mg/kg) in corn oil vehicle.

In a dermal genotoxicity study, homozygous transgenic female Tg.AC mice were given topical applications of ethyl acrylate at doses of 60, 300, or 600 µmol per mouse at a rate of 3 times/week for 20 weeks (Tice et al., 1997). Peripheral blood leukocytes were assessed for DNA damage (single-strand breaks, alkali labile sites, DNA cross linking) at Weeks 4, 8, 12, 16, and 20. Polychromatic and normochromatic erythrocytes in peripheral blood were evaluated for the presence of micronuclei at Week 20. No blood effects were observed except at cytotoxic doses, which induced cell proliferation in keratinocytes. Skin irritation was observed at the site of ethyl acrylate administration.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfD VALUES FOR ETHYL ACRYLATE

Numerous studies have demonstrated that ethyl acrylate produces forestomach lesions (primarily irritation and hyperplasia) by oral exposure in rodents. This includes studies of acute/short-term (Frederick et al., 1990; FDRL, 1986; Ghanayem et al., 1986; NTP, 1986; Ghanayem et al., 1985a, b), subchronic (Ghanayem et al., 1991c; Bernacki et al., 1987a), and chronic (Ghanayem et al., 1994; NTP, 1986) exposure durations, by drinking water and oral gavage. Although some studies have not found forestomach lesions (most notably, the NTP subchronic-duration gavage studies in both rats and mice), the database support for effects in this compartment is overwhelming. There is no evidence of effects on any other tissue or organ in any of the available studies. Table 9 presents a summary of the subchronic and chronic noncancer data that are available.

SUBCHRONIC p-RfD

The available database for subchronic-duration oral route studies includes gavage and drinking water exposure in rats and mice (see Table 9). Five 13-week studies (three in F344 rats and two in B6C3F$_1$ mice) employed gavage dosing as the route of compound administration (Ghanayem et al., 1991c; Bernacki et al., 1987b; NTP, 1986). The subchronic drinking water study in rats (Bernacki et al., 1987a) is identified as a potentially suitable study for quantitative derivation of a provisional subchronic oral reference value, however based upon current standard operating procedure, unpublished principal or influential studies must be peer-reviewed before they can be considered for reference value derivation. Since the Bernacki et al. (1987a) study is an unpublished submission, it is not known if the information has been peer-reviewed. As such, while a subchronic provisional oral reference value cannot be derived here, a "screening-level" evaluation of subchronic oral ethyl acrylate toxicity is provided in Appendix A.

Table 9. Summary of Subchronic and Chronic Oral Noncancer Dose-response Data for Ethyl Acrylate

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration-adjusted[a] NOAEL (mg/kg-d)	Duration-adjusted[a] LOAEL (mg/kg-d)	Responses at the LOAEL	Comments	Reference
Subchronic-duration Studies								
F344 rats (10/sex/dose) Gavage	0, 7, 14, 28, 55, or 110 mg/kg-d; 5 d/wk for 13 wk	110	N/A	79	N/A	No effects on survival or body weight; no gross or histopathologic changes.	Histopathology (including forestomach) was performed only in the control and high-dose groups.	NTP (1986)
F344 rats (10−11 males/ group) Gavage	0, 100, or 200 mg/kg-d, 5 d/wk for 13 wk	N/A	100	N/A	71	Thickening of forestomach wall accompanied by mucosal hyperplasia in all treated animals.	Only forestomach, glandular stomach, and liver were examined.	Ghanayem et al. (1991c)
F344 rats (40 males, 20 females/ group) Drinking water	0, 17, 70, 135, and 249 mg/kg-d (M), and 0, 20, 87, 161, and 293 (F) 7 d/wk for 13 wk	17	70	17	70	Increased relative stomach weights, forestomach gross pathology, and hyperplasia		Bernacki et al. (1987a)
Male F344 rats (20/dose) Gavage	0, 20, 100, 200 mg/kg-d, 5 d/wk for 13 wk	N/A	20	N/A	14	Forestomach hyperplasia		Bernacki et al. (1987b)
B6C3F1 mice (10/sex/dose) Gavage	0, 1.5, 3, 6, 12, or 25 mg/kg-d; 5 d/wk for 13 wk	25	N/A	18	N/A	No effects on survival or body weight; no gross or histopathologic changes.	Histopathology (including forestomach) was performed only in the control and high-dose groups.	NTP (1986)

Table 9. Summary of Subchronic and Chronic Oral Noncancer Dose-response Data for Ethyl Acrylate

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration-adjusted[a] NOAEL (mg/kg-d)	Duration-adjusted[a] LOAEL (mg/kg-d)	Responses at the LOAEL	Comments	Reference
B6C3F1 mice (10/sex/dose) Gavage	0, 12, 25, 50, or 100 mg/kg-d; 5 d/wk for 13 wks	100	N/A	71	N/A	No effects on survival or body weight; no gross or histopathologic changes.	Second study conducted at higher doses because no effects were observed in the first.	NTP (1986)
Chronic-duration studies								
F344 rats (21−28 males/ exposure duration) Gavage	0 or 200 mg/kg-day, 5 d/wk for 6 or 12 mo	N/A	200	N/A	143	Severe forestomach histopathology at sacrifice at the end of exposure	Stop-recovery studies	Ghanayem et al. (1994)
F344 rats (50/sex/dose) Gavage	0, 100, or 200 mg/kg-d; 5 d/wk for 103 wk	N/A	100	N/A	71	Increased incidence and severity of forestomach gross pathology, hyperplasia, and associated lesions.		NTP (1986)
Wistar rats (25/sex/dose) Drinking water	0, 0.5, 5, or 120 mg/kg-d (M), and 0, 0.7, 7, or 180 mg/kg-d (F) daily for 2 yr	M: 120 F: 7	M: N/A F: 180	M: 120 F: 7	M: N/A F: 180	Decreased body weight in females. No treatment-related changes in survival, organ weights, selected hematology and urinary parameters, gross pathology, or histopathology.	Body-weight changes accompanied reduced water intake and food consumption. It is unclear whether forestomach was examined.	Borzelleca et al. (1964)

Table 9. Summary of Subchronic and Chronic Oral Noncancer Dose-response Data for Ethyl Acrylate

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/kg-d)	LOAEL (mg/kg-d)	Duration-adjusted[a] NOAEL (mg/kg-d)	Duration-adjusted[a] LOAEL (mg/kg-d)	Responses at the LOAEL	Comments	Reference
$B6C3F_1$ mice (50/sex/dose) Gavage	0, 100, or 200 mg/kg-d; 5 d/wk for 103 wk	N/A	100	N/A	71	Increased incidence and severity of forestomach gross pathology, hyperplasia, and associated lesions.		NTP (1986)
Beagle dogs (2/sex/dose) Gelatin capsule	0, 0.20, 2.0, and 23 mg/kg-d for 104 wk	23	N/A	22[b]	N/A	No treatment-related changes in survival, organ weights, selected hematology and urinary parameters, or histopathology. Slightly lower body weights in high-dose dogs was associated with decreased food consumption.	Individual and summary data were not given, with the exception of body weight data (means presented only).	Borzelleca et al. (1964)

[a]Adjusted to continuous exposure as follows: $NOAEL_{ADJ}$ = NOAEL × exposure d ÷ 7 d.
[b]Adjusted for step-up dosing procedure used in high dose. See section "ANIMAL STUDIES, Oral Exposure, Chronic-duration Studies" for further details.

N/A = Not applicable.

CHRONIC p-RfD

Chronic-duration oral toxicity studies conducted with ethyl acrylate are shown in Table 9. NTP (1986) performed chronic-duration gavage studies in rats and mice, both of which showed forestomach lesions at a LOAEL of 71 mg/kg-day with no NOAEL identified. Ghanayem et al. (1994) performed a 12-month gavage study in rats that showed forestomach lesions at 143 mg/kg-day, the only dose tested. Borzelleca et al. (1964) conducted chronic-duration studies of ethyl acrylate in rats by drinking water and dogs by gelatin capsules (ethyl acrylate dissolved in corn oil, similar to gavage administration) that found only decreased body weight in female rats (LOAEL = 180 mg/kg-day, NOAEL = 7 mg/kg-day) and no effects in dogs (NOAEL = 22 mg/kg-day). However, organs examined for histopathology in the Borzelleca et al. (1964) studies included "gastroenteric" tissues without further elaboration, and it is not known to what extent individual organs of the gastrointestinal tract (e.g., the forestomach of the rats) were evaluated.

The lowest LOAELs in the chronic-duration studies were identical values of 71 mg/kg-day in the NTP (1986) rat and mouse studies. No NOAEL was identified for either study. The incidences of forestomach hyperplasia, hyperkeratosis, and inflammation in the NTP (1986) rat study (see Table 5) and hyperplasia and hyperkeratosis in the NTP (1986) mouse study (see Table 6) were subjected to BMD modeling using the unadjusted (5 days/week) doses. Appendix B and Table 10 provide a summary of the modeling results. The $BMDL_{10}$ estimated for forestomach hyperkeratosis in male rats (2.3 mg/kg-day) was lower than that for the other endpoints, as shown in Table 10, and was selected as the POD for derivation of the chronic p-RfD.

Because the BMD modeling was done using the unadjusted (5 days/week) doses, the resulting $BMDL_{10}$ is an unadjusted dose; it was adjusted to equivalent continuous exposure as follows:

$$\begin{aligned} BMDL_{10\ ADJ} &= BMDL_{10} \times 5 \text{ days} \div 7 \text{ days} \\ &= 2.3 \text{ mg/kg-day} \times 5 \text{ days} \div 7 \text{ days} \\ &= 1.6 \text{ mg/kg-day} \end{aligned}$$

The **chronic p-RfD of 5×10^{-3}** mg/kg-day for ethyl acrylate was then derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfD} &= BMDL_{10\ ADJ} \div UF_C \\ &= 1.6 \text{ mg/kg-day} \div 300 \\ &= \textbf{5 \times 10^{-3} mg/kg-day} \end{aligned}$$

The UF_C of 300 is composed of the following UFs (see Table 11):

Table 10. Summary of BMDs and BMDLs for Forestomach Endpoints in Rats and Mice Exposed Chronically to Ethyl Acrylate[a]

Endpoint	Species	Best-Fitting Model	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Forestomach hyperkeratosis	Male rat	Log logistic	19.99	2.26
Forestomach hyperplasia	Male rat	Log probit	12.16	9.21
Forestomach inflammation	Male rat	Probit	80.41	63.99
Forestomach hyperkeratosis	Female rat	Multistage (2-degree)	38.07	15.31
Forestomach hyperplasia	Female rat	Multistage (1-degree)	7.63	6.13
Forestomach Hyperkeratosis	Male mouse	Log logistic	16.93	12.06
Forestomach hyperplasia	Male mouse	Log logistic	20.09	14.30
Forestomach Hyperkeratosis	Female mouse	Probit	57.08	45.79
Forestomach hyperplasia	Female mouse	Logistic	64.35	51.71

[a]Source of data: NTP (1986).

Table 11. UFs for the Chronic p-RfD for Ethyl Acrylate

UF	Value	Justification
UF_A	10	For the POD based on increased incidence of forestomach lesions in rats (NTP, 1986), an UF_A of 10 has been applied to account for uncertainty in characterizing the toxicodynamic and toxicokinetic differences between rats and humans following oral ethyl acrylate exposure. Calculation of a human equivalent dose (HED), through application of a dosimetric adjustment factor (DAF) as outlined in EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), could not be applied because the critical effect(s) are at the portal-of-entry.
UF_D	3	A factor of 3 is applied to account for database deficiencies. The toxicological database for oral ethyl acrylate includes high-quality subchronic- and chronic-duration bioassays in two species. One oral developmental study is available, however it lacked information about the dose level at which effects occurred and therefore is not suitable for use in derivation of toxicity values. The database also lacks two-generation reproductive toxicity studies. Nevertheless, the developmental studies with inhalation exposure (Saillenfait et al., 1999; Murray et al., 1981) suggested that developmental toxicity is not more sensitive than systemic toxicity.
UF_H	10	A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
UF_L	1	An UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	An UF_S of 1 has been applied because a chronic-duration study was selected as the principal study.
UF_C	300	

The confidence in the chronic p-RfD for ethyl acrylate is medium as explained in Table 12 below.

Table 12. Confidence Descriptors for the Chronic p-RfD

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	Confidence in the principal study is medium. The rat study (NTP, 1986) was conducted according to standard test guidelines and used a suitable number of animals and appropriate statistical methodology. However, only two doses were tested, and a NOAEL was not identified.
Confidence in database	M	Confidence in the database is medium. The results of the rat study are supported by the mouse study, as well as the Ghanayem et al. (1994) gavage study, and numerous other acute/short-term and subchronic-duration studies, although the subchronic-duration gavage studies by NTP (1986)did not find forestomach lesions in rats or mice. No adequate developmental or multigeneration reproduction studies were located for ethyl acrylate by oral exposure, although inhalation studies of developmental toxicity in rats found mild fetotoxicity at maternally toxic doses.
Confidence in Chronic p-RfD[b]	M	The overall confidence in the Chronic p-RfD is medium.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR ETHYL ACRYLATE

The toxicological database for inhaled ethyl acrylate includes a chronic-duration 24−27-month study in rats and mice with information from interim evaluations at 3, 6, 12, and 18 months (Miller et al., 1985) and two developmental toxicity studies (Saillenfait et al., 1999; Murray et al., 1981). In the chronic-duration study, nasal histopathology was observed in both rats and mice at the same exposure level (102 mg/m^3) after 6 and 27 months. The severity and extent of the histopathology increased with increasing exposure concentration, but there were no appreciable changes in the extent and severity of lesions as the study progressed. Both the rat and mouse studies identified a NOAEL of 21 mg/m^3 (5 ppm) based on nasal histopathology. The developmental studies showed maternal and fetal effects at 614 mg/m^3. A summary of the relevant inhalation data is presented in Table 13.

To provide a basis for comparing the effect levels in the available studies, each was converted to a human equivalent concentration (HEC), adjusting for intermittent dosing and using the dosimetric adjustment appropriate to the observed effect (U.S. EPA, 1994b), as follows:

$$NOAEL_{HEC} = \text{animal NOAEL} \times \text{hours} \div 24 \times \text{days} \div 7 \times \text{dosimetric adjustment}$$

Table 13. Summary of Inhalation Noncancer Dose-response Data for Ethyl Acrylate

Species and Study Type (*n*/sex/group)	Exposure	NOAEL[a] (mg/m^3)	LOAEL[a] (mg/m^3)	Responses at the LOAEL	Reference
F344 Rats (92/ sex/dose) (115/sex/dose) (115/sex/dose) (80/sex/dose) (90/sex/dose)	0 mg/m^3, 6 hr/d, 5 d/wk for 27 mo 102 or 307 mg/m^3 for 27 mo 921 mg/m^3 for 6 mo 0 mg/m^3 for 24 mo 21 mg/m^3 for 24 mo	NOAEL = 21 $NOAEL_{HEC}$ = 0.76	LOAEL = 102 $LOAEL_{HEC}$ = 3.7	Dose-dependent histopathological lesions of the olfactory tract, including respiratory metaplasia.	Miller et al. (1985)
$B6C3F_1$ Mice (84/ sex/dose) (105/sex/dose) (105/sex/dose) (80/sex/dose) (90/sex/dose)	0 mg/m^3, 6 hr/d, 5 d/wk for 27 mo 102 or 307 mg/m^3 for 27 mo 921 mg/m^3 for 6 mo 0 mg/m^3 for 24 mo 21 mg/m^3 for 24 mo	NOAEL = 21 **Respiratory effects** $NOAEL_{HEC}$ = 0.77	LOAEL = 102 **Respiratory effects** $LOAEL_{HEC}$ = 3.8	Dose-dependent histopathological lesions of the olfactory tract, including respiratory metaplasia.	Miller et al. (1985)
Developmental toxicity studies					
Sprague-Dawley Rats (33 females/ group)	0, 205, or 614 mg/m^3, 6 hr/d on GDs 6−15	**Maternal and developmental** NOAEL = 205 $NOAEL_{HEC}$ = 51	**Maternal and developmental** LOAEL = 614 $LOAEL_{HEC}$ = 154	Significantly decreased maternal body-weight gain. Fetal malformations including hypoplastic tail.	Murray et al. (1981)

Table 13. Summary of Inhalation Noncancer Dose-response Data for Ethyl Acrylate

Species and Study Type (*n*/sex/group)	Exposure	NOAEL[a] (mg/m^3)	LOAEL[a] (mg/m^3)	Responses at the LOAEL	Reference
Sprague-Dawley rats (20 females/group)	0, 102, 205, 409, or 820 mg/m^3, 6 hr/d on GDs 6−20	**Maternal and developmental** NOAEL = 409 $NOAEL_{HEC}$ = 102	**Maternal and developmental** LOAEL = 820 $LOAEL_{HEC}$ = 205	Significantly decreased maternal body-weight gain. Mean fetal body-weight reductions of 7−8%.	Saillenfait et al. (1999)

[a]HEC calculated as follows: $NOAEL_{HEC}$ = NOAEL × exposure hr ÷ 24 hr × exposure d/7 d × dosimetric adjustment. For nonrespiratory effects, the dosimetric adjustment is the ratio of the animal:human blood:gas partition coefficients; in the absence of experimental values, a default value of 1 is used (U.S. EPA, 1994b). For nasal lesions, the regional gas dose ratio for extrathoracic effects ($RGDR_{ET}$) is used (U.S. EPA, 1994b). The $RGDR_{ET}$ for rats in the chronic-duration toxicity study is 0.204; for mice, it is 0.206. These values were calculated using the equations and default body weights in U.S. EPA (1994b).

N/A = Not applicable.

For ethyl acrylate, nasal lesions were among the most sensitive effects in rats and mice of both sexes in the chronic-duration studies. Therefore, dosimetric adjustments for the effect levels associated with these studies were performed using the Regional Gas Dose Ratio for extrathoracic effects ($RGDR_{ET}$) (using Equation 4-18 and default values from U.S. EPA, 1994b), as follows:

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

where:

V_E = minute volume (L/minute)
= 0.211 L/ minute for F344 rats (based on default body weight of 304 g in a chronic-duration study, males and females combined), 0.043 L/ minute for $B6C3F_1$ mice (based on default body weight of 36.3 g in a chronic-duration study, males and females combined) and 13.8 L/ minute for humans

SA_{ET} = surface area of the extrathoracic region (cm^2)
= 15 cm^2 for rats, 3 cm^2 for mice, 200 cm^2 for humans

Systemic effects, primarily effects on body weight, were also observed in some of the ethyl acrylate studies. For these extrarespiratory end points, the dosimetric adjustments were made using the ratio of the animal:human blood:gas partition coefficients (U.S. EPA, 1994b). Blood:gas partition coefficients for ethyl acrylate were not located in the available literature; thus, the default ratio of 1.0 was used, as specified in the guidance (U.S. EPA, 1994b).

SUBCHRONIC AND CHRONIC p-RfC

Table 13 includes the HECs calculated for inhalation data on ethyl acrylate. The lowest $LOAEL_{HEC}$ values (~3.7 mg/m^3) were those associated with nasal lesions in rats and mice in the Miller et al. (1985) chronic-duration study, and the corresponding lower $NOAEL_{HEC}$ is 0.76 mg/m^3. Because the critical effect occurred at the portal of entry, and there were no appreciable changes in the extent and severity of lesions over time as the study progressed, the same toxicity value was estimated for both subchronic and chronic p-RfCs. The nasal histopathology data in rats and mice as presented by Miller et al. (1985) are not suitable for BMD modeling because they are presented only as cumulative percentages based on unspecified numbers of animals sacrificed and dying at various subchronic and chronic time points during the study. Therefore, the $NOAEL_{HEC}$ of 0.76 mg/m^3 from the rat study was selected as the POD for derivation of both the subchronic and chronic p-RfC.

The provisional **subchronic and chronic p-RfCs of 8×10^{-3} mg/m^3** for ethyl acrylate, based on the $NOAEL_{HEC}$ of 0.76 mg/m^3 for olfactory tract histopathology in rats exposed for 6−27 months (Miller et al., 1985), is derived as follows:

Subchronic and Chronic p-RfCs = $NOAEL_{HEC} \div UF_C$
= 0.76 $mg/m^3 \div 100$
= **8×10^{-3} mg/m^3**

The UF_C of 100 is composed of the following UFs (see Table 14):

Table 14. UFs for the Subchronic and Chronic p-RfCs for Ethyl Acrylate

UF	Value	Justification
UF_A	3	A factor of 3 is applied for animal-to-human extrapolation because derivation of a HEC from the animal data partially adjusts for interspecies sensitivity (U.S. EPA, 1994b).
UF_D	3	A factor of 3 is applied to account for database deficiencies. The toxicological database for inhaled ethyl acrylate includes comprehensive chronic-duration bioassays in two species (Miller et al., 1985). Two inhalation developmental toxicity studies are also available, although both were conducted in rats (Saillenfait et al., 1999; Murray et al., 1981). The database lacks a multigeneration reproductive toxicity study and a developmental study in a second species; thus, a factor of 3 was applied for database inadequacies.
UF_H	10	A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
UF_L	1	An UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a NOAEL.
UF_S	1	A factor of 1 is applied because the irritant effects of ethyl acrylate are considered correlated with exposure concentration rather than duration of exposure.
UF_C	300	

The confidence in the subchronic and chronic p-RfCs for ethyl acrylate is medium as explained in Table 15 below.

Table 15. Confidence Descriptors for the Subchronic and Chronic p-RfCs

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	Confidence in the principal study is medium. The Miller et al. (1985) study used an appropriate number of animals from two species and a wide range of inhalation exposure levels and performed a comprehensive evaluation of endpoints. Although NOAEL and LOAEL values were identified, the data were not reported in a manner suitable for BMD modeling.
Confidence in database	M	Confidence in the database is medium. Although two inhalation developmental toxicity studies have been conducted in rats, a multigeneration reproductive toxicity study and a developmental study in a second species are lacking.
Confidence in Chronic p-RfD[b]	M	The overall confidence in the Subchronic and Chronic p-RfCs is medium.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ETHYL ACRYLATE

WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the available evidence for ethyl acrylate supports the "*Suggestive Evidence of Carcinogenic Potential*" descriptor via oral exposure at doses that induce severe irritation and cell proliferation. With respect to the inhalation route of exposure, the available evidence for ethyl acrylate supports the "*Not Likely to be Carcinogenic to Humans*". This WOE descriptor is based on the following information:

1. Ethyl acrylate causes forestomach tumors (but no other tumors) in both sexes of two species (in rats and mice) after gavage administration;
2. Stop-recovery studies in rats have demonstrated that ethyl acrylate only causes forestomach tumors with gavage exposure >6 months to doses that cause irritation and regenerative hyperplasia;
3. No tumors were observed in a chronic-duration drinking water study in rats that included a dose shown to be tumorigenic by administration in corn oil by gavage;
4. No tumors were observed in two species and sexes of animals exposed to ethyl acrylate over a lifetime via inhalation;
5. Ethyl acrylate caused forestomach tumors in rats and mice by a nongenotoxic mode of action that involves irritation of the mucosa, inflammation, and regenerative hyperplasia leading to neoplasia. It is not genotoxic except at exposures that also cause cytotoxicity; and
6. There is no information about ethyl acrylate carcinogenicity at low dose levels relevant to potential human exposures.

This conclusion is consistent with that of the NTP (2011) *12th Report on Carcinogens*. Although NTP (1986) initially identified ethyl acrylate as a carcinogen based on forestomach tumors in rats and mice in gavage studies, NTP (2005) later delisted ethyl acrylate from the *11th Report on Carcinogens* because, "forestomach tumors induced in animal studies were seen only when the chemical was administered by gavage at high concentrations of ethyl acrylate, that induced marked local irritation and cellular proliferation, and because significant chronic human exposure to high concentrations of ethyl acrylate monomer is unlikely."

There are no human data on the carcinogenic effects of ethyl acrylate. In 2-year gavage studies with rats and mice, increased incidences of squamous cell papillomas, squamous cell carcinomas, and/or combined papillomas and carcinomas of the forestomach were observed in rats and mice at doses of 71 and 143 mg/kg-day, with higher tumor incidences being reported in rats (NTP, 1986). No tumors in any other target organ or tissue were observed in these gavage studies. There are extensive mechanistic data from numerous studies, as well as a series of well-conducted stop exposure-recovery experiments, indicating that the mode of carcinogenic action in the forestomach is via severe cytotoxicity resulting in sustained reparative cell proliferation. The cytotoxicity manifests as significant (both in terms of severity and extent of distribution) forestomach hyperplasia and other associated lesions caused by continuous high-dose gavage dosing for at least half the lifetime of the rodent (Ghanayem et al., 1994, 1993).

No tumors were observed in a 2-year drinking water study with rats at approximate doses up to 180 mg/kg-day (Borzelleca et al., 1964) or in a 2-year capsule bioassay with dogs at doses up to 22 mg/kg-day (Borzelleca et al., 1964), although group sizes (2 dogs/sex/dose) were very small in the dog study. Inhalation exposure to ethyl acrylate in chronic-duration bioassays did not induce tumors at any site in rats or mice of both sexes exposed to vaporized concentrations up to 307 mg/m^3 (Miller et al., 1985).

Numerous genetic toxicology studies demonstrate that ethyl acrylate is not genotoxic except at exposure levels that are also cytotoxic. In *S. typhimurium* mutagenicity assays, ethyl acrylate tested negative in numerous studies and tester strains, with and without metabolic activation (Emmert et al., 2006; Zeiger et al., 1992; Waegemaekers and Bensink, 1984; Rohm and Haas Co, 1980). Positive results in mutagenicity assays in L5178Y cells were shown to be due to clastogenic effects associated with cytotoxicity (Ciaccio et al., 1998; Dearfield et al., 1991; Moore et al., 1989, 1988). Ciaccio et al. (1998) presented data that the effects resulted from NPSH depletion and mitochondrial membrane impairment and not by direct interaction with DNA. No DNA adducts were observed in the rat forestomach in an in vivo study at gavage doses up to 400 mg/kg (Ghanayem et al., 1987). DNA damage was not induced in a second in vivo study from another laboratory at gavage doses ranging from 5 to 200 mg/kg (Morimoto et al., 1991), as cited in (ECETOC, 1994).

MODE-OF-ACTION DISCUSSION

The U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment* defines mode of action as a sequence of key events and processes, starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes and resulting in cancer formation. Toxicokinetic processes leading to the formation or distribution of the active agent (i.e., parent material or metabolite) to the target tissue are not part of the mode of action. Examples of possible modes of carcinogenic action for a given chemical include mutagenic, mitogenic, antiapoptotic (inhibition of programmed cell death), cytotoxic with reparative cell proliferation, and immunologic suppression.

Key Events

The available data support the following key events in the mode of action for ethyl acrylate-induced forestomach tumors in rodents: (1) marked depletion of glutathione and consequent impairment of the major detoxification pathway in the forestomach after gavage administration; (2) cytotoxicity in the form of cellular injury, necrosis, and death; and (3) significantly increased reparative cell replication. Cell proliferation is believed to increase tumor formation through one or more of the following mechanisms (Butterworth et al., 1995; Barrett, 1993):

- Increased number of spontaneous initiations occurring during replication
- Inhibition of apoptosis of initiated cells
- Promotion of clonal expansion of initiated cells
- Increased rate of neoplastic progression
- Selective growth advantage of initiated cells
- Reduced time available for DNA repair mechanisms

Strength, Consistency, and Specificity of Association

An abundance of information supports the association between ethyl acrylate and the key events outlined above. Dose-related depletion of glutathione in the rat forestomach was demonstrated after gavage administration in several studies (Frederick et al., 1990; de Bethizy et al., 1987; NTP, 1986). While glutathione depletion was also observed in the glandular stomach after gavage dosing, the magnitude of effect was much less in the glandular stomach compared with the forestomach, either due to more concentrated exposure in the forestomach or greater sensitivity to ethyl acrylate (Frederick et al., 1990; de Bethizy et al., 1987; NTP, 1986). One study also demonstrated that glutathione depletion did not occur after exposure via drinking water at doses shown to deplete glutathione after gavage (Frederick et al., 1990). Increases in cell proliferation in the forestomach were shown in two studies of ethyl acrylate administered via gavage (Gillette and Frederick, 1993; Ghanayem et al., 1991c). In contrast, little effect on cell proliferation was observed in the glandular stomach (Gillette and Frederick, 1993) or liver (Ghanayem et al., 1991c). Finally, the association between gavage administration of ethyl acrylate and both injury and hyperplasia in the forestomach has been demonstrated in both rats and mice in numerous studies (Ghanayem et al., 1994, 1991c; Frederick et al., 1990; FDRL, 1986; Ghanayem et al., 1986; NTP, 1986).

Dose-response Concordance

Forestomach tumors have been observed only at doses where proposed precursor effects occur and are clearly evident. NPSH depletion occurs at doses ≥2 mg/kg-day but reaches maximum depletion (to about 10% of control values 1 hour after dosing) at 100 mg/kg-day (Frederick et al., 1990; de Bethizy et al., 1987; NTP, 1986). Forestomach hyperplasia has been observed at doses from 20 to 200 mg/kg-day, but the effect was seen in nearly all animals treated at ≥100 mg/kg-day. Statistically significant increases in the incidence of forestomach tumors (papillomas and carcinomas) were observed after 2 years of gavage dosing at ≥100 mg/kg-day (NTP, 1986) and after 12 months at 200 mg/kg-day followed by 9 months of recovery time (Ghanayem et al., 1994). Table 16 shows the dose-response concordance between tumors and other lesions in the forestomach.

Temporal Relationships

A series of stop-recovery studies have demonstrated that gavage administration of ethyl acrylate at 200 mg/kg-day to rats results in marked forestomach hyperplasia after as little as two weeks of exposure (Ghanayem et al., 1986). Table 17 outlines the temporal relationships among forestomach hyperplasia, hyperkeratosis, and papilloma and carcinoma formation in several stop-recovery studies (Ghanayem et al., 1994, 1991c) and the chronic-duration rat study (NTP, 1986). These studies indicate that ethyl acrylate-induced effects on the forestomach regress with time after exposures as long as 6 months (Ghanayem et al., 1994). In contrast, with exposure for 12 months or more, papilloma and carcinoma formation is evident, even when the severity of hyperplasia has improved (Ghanayem et al., 1994; NTP, 1986). These data are consistent with the hypothesis that duration of exposure to ethyl acrylate has to be sufficiently long to allow for spontaneous mutation and/or clonal expansion of initiated cells.

Table 16. Dose-response Concordance of Key Forestomach Effects in Male Rats Treated via Gavage

Reference	Exposure Duration	Endpoint	Dose (mg/kg-d)[a]				
			0	20−28	50−55	100−110	200
NTP (1986)	2 yr	Carcinoma	0/48	-	-	2/47	5/50
		Papilloma	0/48	-	-	4/47	9/50
		Hyperkeratosis	0/50	-	-	37/50	46/50
		Hyperplasia	1/50	-	-	41/50	46/50
		Inflammation	1/50	-	-	8/50	28/50
Ghanayem et al. (1991c)	13 wk, no recovery	Hyperplasia	0/10	-	-	10/10	11/11
	13 wk, 8 wk recovery	Hyperplasia	0/10	-	-	1/10	6/10
	13 wk, 19 mo recovery	Hyperplasia	2/35	-	-	2/26	9/29
NTP (1986)	13 wk	Hyperplasia	0/10	0/10	0/10	0/10	-
Frederick et al. (1990)	14 d	Hyperplasia	0/10	3/10	7/10	10/10	10/10
		Hyperkeratosis	0/10	3/10	8/10	10/10	10/10
Ghanayem et al. (1986)	14 d, no recovery	Hyperplasia	0/24	-	-	12/12	12/12
		Hyperkeratosis	0/24	-	-	12/12	12/12
	14 d, 7 d recovery	Hyperplasia	0/24	-	-	6/8	-
		Hyperkeratosis	0/24	-	-	6/8	-
	14 d, 14 d recovery	Hyperplasia	0/24	-	-	0/8	8/8
		Hyperkeratosis	0/24	-	-	0/8	8/8
	14 d, 28 d recovery	Hyperplasia	0/24	-	-	-	8/8
		Hyperkeratosis	0/24	-	-	-	0/8

[a]Doses in this table are the administered dose and are not duration-adjusted.

"-" indicates that there is no data for this endpoint at this dose/duration combination.

Table 17. Temporal Relationships Among Forestomach Effects in Male Rats Exposed via Gavage to 200-mg/kg-day Ethyl Acrylate for Various Exposure Durations and Untreated Recovery Periods

Recovery Time	Exposure Duration				
	4 Wk[a]	13 Wk[b]	26 Wk[c]	52 Wk[c]	103 Wk[d]
None	Hyperplasia (6/6)[e] Hyperkeratosis (6/6)	Severe hyperplasia (11/11)	Moderate hyperplasia (5/5)	Marked hyperplasia (5/5)	Hyperplasia (46/50) Hyperkeratosis (37/50) Inflammation (28/50) Papillomas (9/50) Carcinomas (5/50)
6−8 wk	Hyperplasia (4/4) Hyperkeratosis (4/4)	Mild hyperplasia (6/10)	Hyperplasia (0/5)	Minimal hyperplasia (5/5) Papillomas (2/5)	NE
36 wk	NE	NE	NE	Minimal hyperplasia (10/13) Papillomas (1/13) Carcinomas (3/13)	NE
60 wk	NE	NE	Minimal hyperplasia (1/18)	NE	NE
76 wk	NE	Mild hyperplasia (9/29)	NE	NE	NE

[a]FDRL (1986).
[b]Ghanayem et al. (1994).
[c]Ghanayem et al. (1994).
[d]NTP (1986).
[e]Observed effect (incidence).

NE = not evaluated.

Biological Plausibility and Coherence

A cytotoxicity and regenerative hyperplasia mode of action for ethyl acrylate-induced forestomach tumors is plausible and consistent with the available data based on the following lines of evidence:

1. ethyl acrylate has been shown to increase cell proliferation in the rat forestomach—but not the liver—at tumorigenic doses administered by gavage (Gillette and Frederick, 1993; Ghanayem et al., 1991c);
2. nonneoplastic changes observed after ethyl acrylate exposure are largely limited to point-of-contact lesions (both in the forestomach after oral exposure and in the nasal passages after inhalation exposure) reflecting irritation, inflammation, and regenerative hyperplasia;
3. withdrawal of exposure results in regression of these lesions when the duration of exposure is less than 12 months;

4. no tumors were observed in a drinking water study (Borzelleca et al., 1964) at a dose that was tumorigenic by gavage, possibly due to the fact that the dose to the forestomach was not as concentrated in the drinking water study.

Conclusion

The database of genotoxicity, mechanistic, and stop-recovery studies for ethyl acrylate supports a mode of action for forestomach tumors induced via depletion of forestomach glutathione, induction of cytotoxicity and regenerative hyperplasia, and increases in spontaneous nonspecific mutation and/or clonal expansion of initiated cells. Long-term exposure studies indicate that prolonged exposure for at least 12 months at doses causing marked irritation and hyperplasia is a prerequisite for tumor formation, and that exposure at doses that are not associated with these effects are unlikely to result in tumors.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Oral Exposure

The forestomach tumors observed in rats and mice (Ghanayem et al., 1994; NTP, 1986) were observed only at high doses of ethyl acrylate administered by gavage for >6 months. Exposure to similar daily doses via drinking water for 2 years did not result in tumor formation (Borzelleca et al., 1964). Prolonged human exposure to high concentrations of ethyl acrylate, such as those used in the gavage studies (Ghanayem et al., 1994; NTP, 1986) is unlikely. According to the NTP (2011) *12th Report on Carcinogens*, the irritant properties of ethyl acrylate would make chronic human exposure to high concentrations of ethyl acrylate via the oral route of exposure unlikely. Supporting this assertion, there was a dose-related decrease in water consumption in both of the rat drinking water studies reviewed in this document (Bernacki et al., 1987a; Borzelleca et al., 1964). The tumor incidence data from the high concentration gavage studies are not considered suitable for quantitative estimation of cancer risk for ethyl acrylate at the low doses likely to be encountered by humans. The lack of sufficient information about the potential carcinogenic activity of ethyl acrylate at lower doses that do not induce local irritation precludes derivation of a quantitative estimate of cancer risk for ethyl acrylate by oral exposure.

Inhalation Exposure

Derivation of a quantitative estimate of cancer risk for ethyl acrylate by inhalation exposure is precluded by the lack of data.

APPENDIX A. DERIVATION OF A SCREENING SUBCHRONIC ORAL VALUE FOR ETHYL ACRYLATE (CASRN 140-88-5)

For reasons noted in the derivation section of this document, it is inappropriate to derive a subchronic oral p-RfD for ethyl acrylate based on the Bernacki et al. (1987a) 13-week drinking water rat study. Specifically, as an unpublished, presumably non-peer-reviewed submission, any useful data provided in such a reference is currently deemed inappropriate for the derivation of provisional toxicity values. However, the qualitative and quantitative information in the Bernacki et al. (1987a) rat study may be used to support derivation of an oral screening value for ethyl acrylate (CASRN 140-88-5) that may be of use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix. Information contained in an appendix receives the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

SCREENING SUBCHRONIC ORAL p-RfD

The available database for subchronic-duration studies includes gavage and drinking water exposure in rats and mice (see Table 9). Five 13-week studies (three in F344 rats and two in B6C3F$_1$ mice) employed gavage dosing as the route of compound administration (Ghanayem et al., 1991c; Bernacki et al., 1987b; NTP, 1986). In one rat study and two mouse studies conducted by NTP (1986), no effects in any organs were observed. Duration-adjusted NOAELs of 79 mg/kg-day for the rat study and 71 mg/kg-day for the two mouse studies combined were identified; no corresponding LOAELs were available from the data. In the rat study by Ghanayem et al. (1991c), dose-dependent gross and microscopic pathology of the forestomach were observed at 71 and 143 mg/kg-day, using the same dosing regimen as the NTP (1986) studies. The LOAEL was 71 mg/kg-day and a NOAEL could not be identified. In the rat study by Bernacki et al. (1987b), dose-dependent gross and microscopic pathology of the forestomach and increased stomach weights were observed at 14, 71, and 143 mg/kg-day. The LOAEL was 14 mg/kg-day based on forestomach hyperplasia, and a NOAEL could not be identified. A sixth study, in which ethyl acrylate was administered in drinking water daily for 13 weeks to male and female F344 rats (Bernacki et al., 1987a), showed (1) dose- and time-related increases in absolute and relative stomach weights throughout the study; (2) gross pathology of the forestomach at interim sacrifices (Weeks 1, 2, and 4) but not at terminal sacrifice; and (3) dose-dependent histopathology ranging from minimal hyperplasia at lower doses to mild-to-moderate hyperplasia, accompanied by hyperkeratosis, at higher doses (Bernacki et al., 1987a). No effects were observed in the glandular stomach. The LOAEL for this drinking water study was 70 mg/kg-day, with a corresponding NOAEL of 17 mg/kg-day. The severity and extent of distribution of lesions in this study were significantly less than those seen in the gavage studies (Ghanayem et al., 1991c; Bernacki et al., 1987b). It is not readily apparent why the subchronic-duration NTP gavage studies did not produce forestomach lesions, given that such lesions were observed in both the shorter and longer duration NTP studies and also in the other subchronic-duration studies at identical doses (even by drinking water exposure).

Across all of the available subchronic duration studies, the lowest LOAEL was 14 mg/kg-day for forestomach effects in the Bernacki et al. (1987b) gavage study, and a NOAEL was not identified. However, this potential point of departure (POD) was not selected due to an apparent enhanced sensitivity for forestomach injury; as illustrated in Table 9, all other available subchronic duration studies, including those in the same species of rat as used in the Bernacki et al. (1987b) gavage study, resulted in LOAELs that were consistently 5-fold higher, or, were NOAELs in other studies, species, or exposure regimens (e.g., drinking water). For example, in the Bernacki et al. (1987a) drinking water study, a LOAEL of 71 mg/kg-day and a NOAEL of 17 mg/kg-day for forestomach effects were identified. Although this suggests that the Bernacki et al. (1987b) forestomach effects following gavage were more sensitive than the forestomach effects from the Bernacki et al. (1987a) drinking water study, it may also reflect the different means of dosing in the two studies. Therefore, it was considered appropriate to perform benchmark dose modeling of the Bernacki et al. (1987a) drinking water data to identify the POD even though the Bernacki et al. (1987b) gavage data indicated greater sensitivity. This decision is supported by a 2-week study (Frederick et al., 1990) using both drinking water and gavage dosing regimens that also showed greater severity of forestomach lesions with gavage dosing. Bernacki et al. (1987a) reported incidences by severity score (minimal, mild, and moderate) as well as total numbers affected; the total numbers of animals affected with hyperplasia at each dose were used in the modeling. Appendix B provides a summary of the modeling results. The $BMDL_{10}$ estimated for forestomach hyperplasia in male rats was 17 mg/kg-day, which is identical to the NOAEL of 17 mg/kg-day identified for males in this study. The $BMDL_{10}$ estimated for forestomach hyperplasia in female rats was 31 mg/kg-day. Because the data were from a drinking water study with continuous exposure, these $BMDL_{10}$ values apply to continuous exposure directly without any further duration adjustment.

The $BMDL_{10}$ calculated for the data in male rats (17 mg/kg-day) was selected as the POD for the derivation of the subchronic p-RfD. The screening subchronic oral p-RfD for ethyl acrylate was derived as follows:

$$\textbf{Screening Subchronic Oral p-RfD} = BMDL_{10} \div UF_C$$
$$= 17 \text{ mg/kg-day} \div 300$$
$$= \mathbf{6 \times 10^{-2} \text{ mg/kg-day}}$$

The composite uncertainty factor (UF_C) of 300 is composed of the following UFs (see Table A-1):

Table A-1. UFs for the Screening Subchronic Oral p-RfD for Ethyl Acrylate

UF	Value	Justification
UF_A	10	For the POD based on increased incidence of forestomach hyperplasia in rats (Bernacki et al., 1987a), an UF_A of 10 has been applied to account for uncertainty in characterizing the toxicodynamic and toxicokinetic differences between rats and humans following oral ethyl acrylate exposure. Calculation of a human equivalent dose (HED), through application of a dosimetric adjustment factor (DAF) as outlined in EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), *could not* be applied because the critical effect is at the portal-of-entry.
UF_D	3	A factor of 3 is applied to account for database deficiencies. The toxicological database for oral ethyl acrylate includes high-quality subchronic- and chronic-duration bioassays in two species. One oral developmental study is available, however it lacked information about the dose level at which effects occurred and therefore is not suitable for use in derivation of toxicity values. The database also lacks two-generation reproductive toxicity studies. Nevertheless, the developmental studies with inhalation exposure (Saillenfait et al., 1999; Murray et al., 1981) suggested that developmental toxicity is not more sensitive than systemic toxicity.
UF_H	10	A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human response are insufficient.
UF_L	1	An UF_L of 1 has been applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL.
UF_S	1	An UF_S of 1 has been applied because a subchronic-duration study was selected as the principal study.
UF_C	300	

The confidence in the screening subchronic p-RfD for ethyl acrylate is low as explained in Table A-2 below.

Table A-2. Confidence Descriptors for the Screening Subchronic Oral p-RfD

Confidence Categories	Designation[a]	Discussion
Confidence in study	L	Confidence in the principal study is low. The Bernacki et al. (1987a) drinking water study used a wide range of doses and an acceptable number of animals and conducted a comprehensive evaluation of appropriate end points, but was not published in the peer-reviewed literature.
Confidence in database	M	Confidence in the database is medium. The results of the drinking water study are supported by the Ghanayem et al. (1991c) subchronic-duration gavage study and numerous other acute/short-term and chronic-duration studies. However, subchronic-duration gavage studies by NTP (1986) did not find forestomach lesions in rats or mice. No adequate developmental or multigeneration reproduction studies were located for ethyl acrylate by oral exposure, although inhalation studies of developmental toxicity in rats found only mild fetotoxicity at maternally toxic doses.
Confidence in chronic p-RfD[b]	L	The overall confidence in the screening subchronic oral p-RfD is low.

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

APPENDIX B. DETAILS OF BENCHMARK DOSE MODELING FOR SCREENING SUBCHRONIC p-RfD

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 BMDL is selected as the point of departure when the difference between the BMDLs estimated from these models is more three-fold (unless it is an outlier); otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) is chosen. In accordance with U.S. EPA (2012b) guidance, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with a BMR of 10% extra risk are calculated for all models.

Model-Fitting Results for Forestomach Hyperplasia in Male and Female Rats (Bernacki et al., 1987a)

The procedure outlined above was applied to the data (see Table 3) for forestomach hyperplasia in male and female rats exposed subchronically to ethyl acrylate via drinking water for 13 weeks (Bernacki et al., 1987a). All models provided adequate fit to both data sets when assessed by the overall χ^2 goodness of fit p-value (see Tables B-1 and B-2). However, inspection of the scaled residuals showed that fit of the 1-degree multistage/quantal linear model was poor in the low-dose region close to the BMR for both data sets (scaled residuals of approximately -2.0 for both). Therefore, these models were dropped from further consideration. For both data sets, the $BMDL_{10}$s from the remaining models differed by less than 3-fold, so the models with the lowest AICs were selected. For male rats, the gamma and log-logistic models had identical AICs; therefore, an average of the $BMDL_{10}$ from the gamma model and the $BMDL_{10}$ from the log-logistic model is used for forestomach hyperplasia in male rats. The BMD_{10} and $BMDL_{10}$ based on the gamma model were 42 and 16 mg/kg-day, respectively; the BMD_{10} and $BMDL_{10}$ from the log-logistic model were 57 and 18 mg/kg-day, respectively. The average of the $BMDL_{10}$ values is 17 mg/kg-day. Fit of the gamma model to the data is shown in Figure B-1. Fit of the log-logistic model to the data is shown in Figure B-2. For female rats, the log-logistic model had the lowest AIC and was selected as the best fitting. The BMD_{10} and $BMDL_{10}$ for forestomach hyperplasia in female rats were 76 and 31 mg/kg-day, respectively. Model fit is shown in Figure B-3. Because the data were from a drinking water study with continuous exposure, these BMD_{10} and $BMDL_{10}$ values apply to continuous exposure directly without any further adjustment.

Table B-1. Model Predictions for Forestomach Hyperplasia in Male Rats Treated with Ethyl Acrylate in the Drinking Water for 13 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	***4***	***0.00***	***1.00***	***12.01***	***41.86***	***15.81***
Logistic	3	0.00	1.00	14.01	60.72	21.38
Log-Logistic[c]	***4***	***0.00***	***1.00***	***12.01***	***57.36***	***17.67***
Log-Probit[c]	3	0.00	1.00	14.01	52.66	16.87
Multistage (degree = 1)[d]	4	4.95	0.29	20.46	5.36	3.48
Multistage (degree = 2)[d]	4	1.00	0.91	13.88	18.82	9.18
Multistage (degree = 3)[d]	4	0.23	0.99	12.46	28.54	11.91
Multistage (degree = 4)[d]	4	0.06	1.00	12.12	35.48	12.90
Probit	3	0.00	1.00	14.01	52.78	19.37
Weibull[b]	3	0.00	1.00	14.01	51.08	15.09
Quantal-Linear	4	4.95	0.29	20.46	5.36	3.48

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

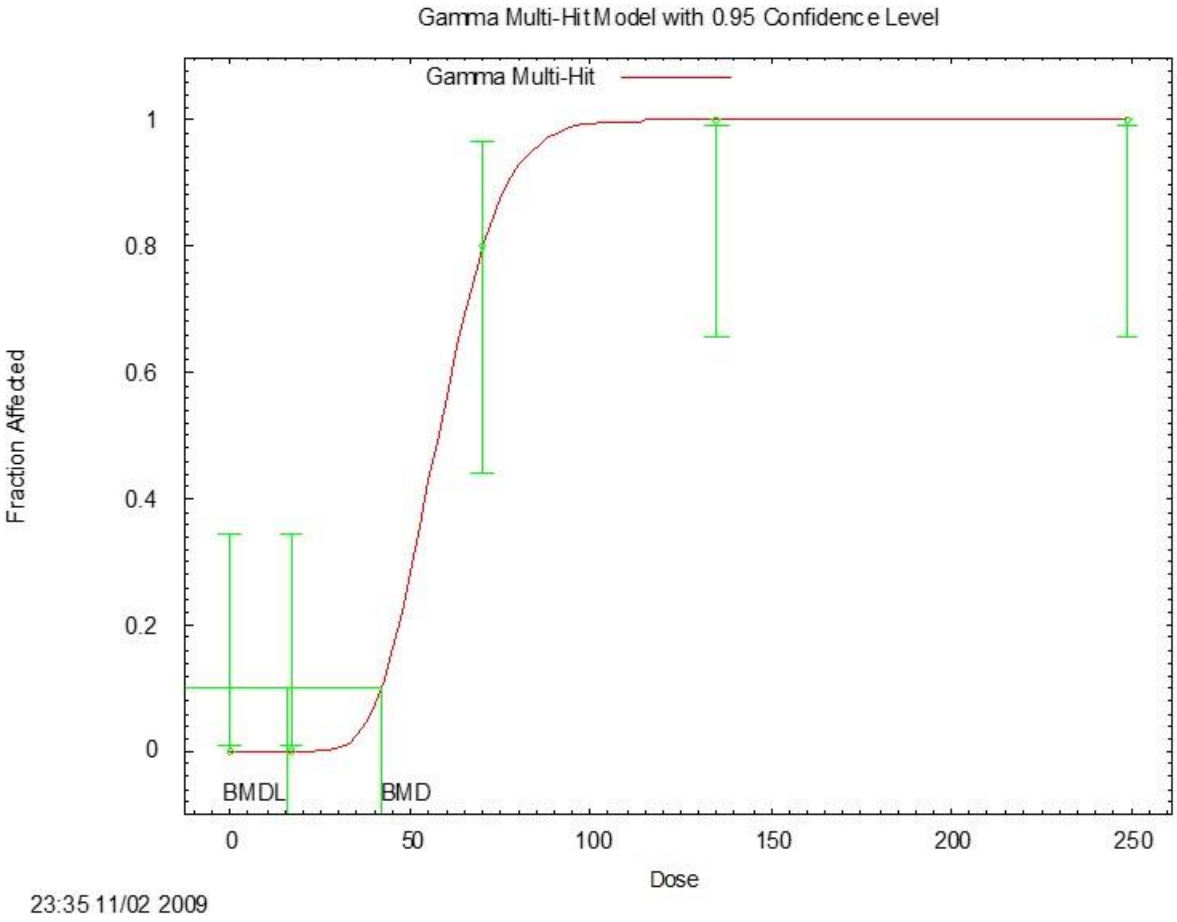
AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the dose/concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD.

Table B-2. Model Predictions for Forestomach Hyperplasia in Female Rats Treated with Ethyl Acrylate in the Drinking Water for 13 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	3	1.06	0.79	25.42	60.16	24.86
Logistic	3	2.75	0.43	26.94	34.19	19.84
Log-Logistic[c]	***3***	***1.05***	***0.79***	***25.40***	***75.65***	***30.94***
Log-Probit[c]	2	1.05	0.59	27.40	73.64	27.93
Multistage (degree = 1)[d]	3	6.03	0.11	33.89	8.40	5.53
Multistage (degree = 2)[d]	3	2.05	0.56	27.19	28.56	14.18
Multistage (degree = 3)[d]	3	1.21	0.75	25.69	42.86	16.84
Multistage (degree = 4)[d]	3	1.08	0.78	25.45	51.45	16.06
Probit	3	2.76	0.43	27.10	29.40	17.90
Weibull[b]	2	1.05	0.59	27.40	67.53	22.87
Quantal-Linear	3	6.03	0.11	33.89	8.40	5.53

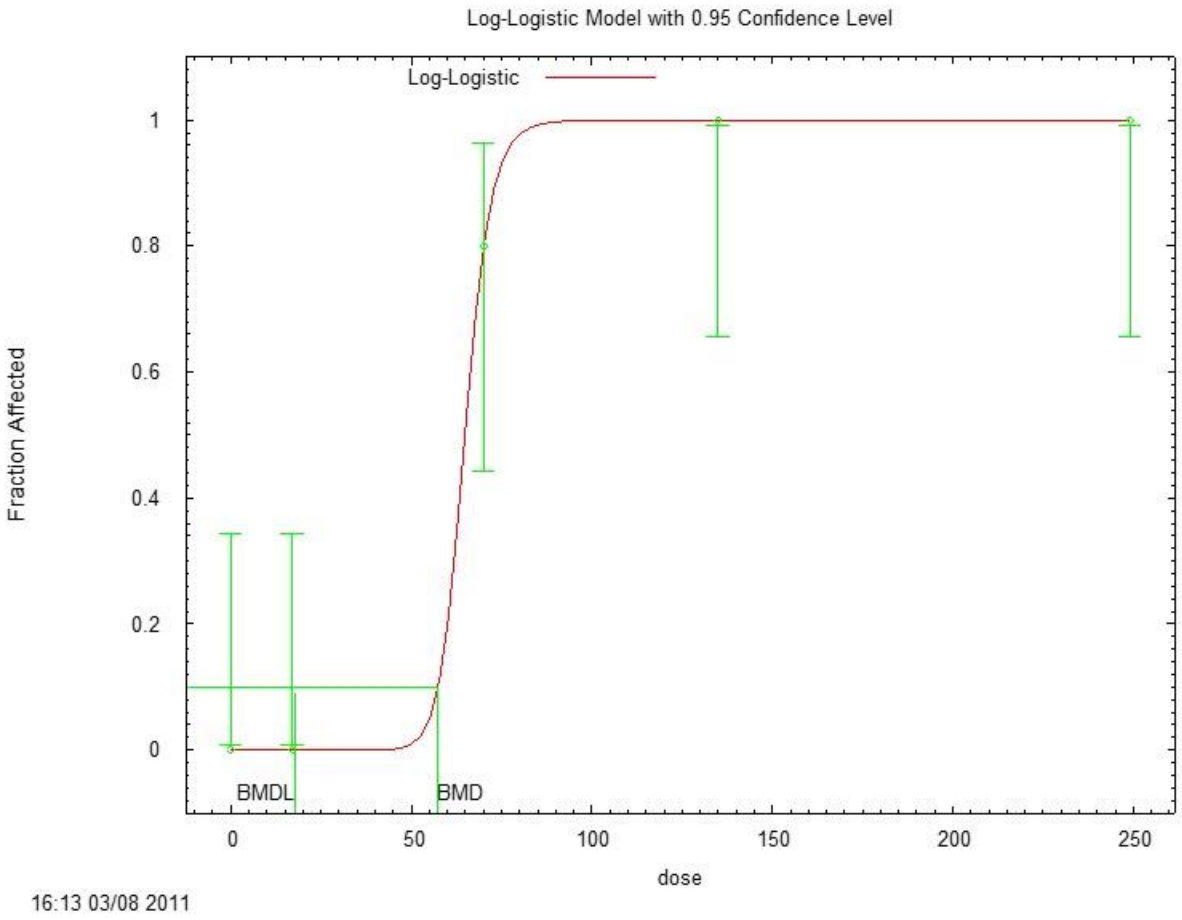
[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



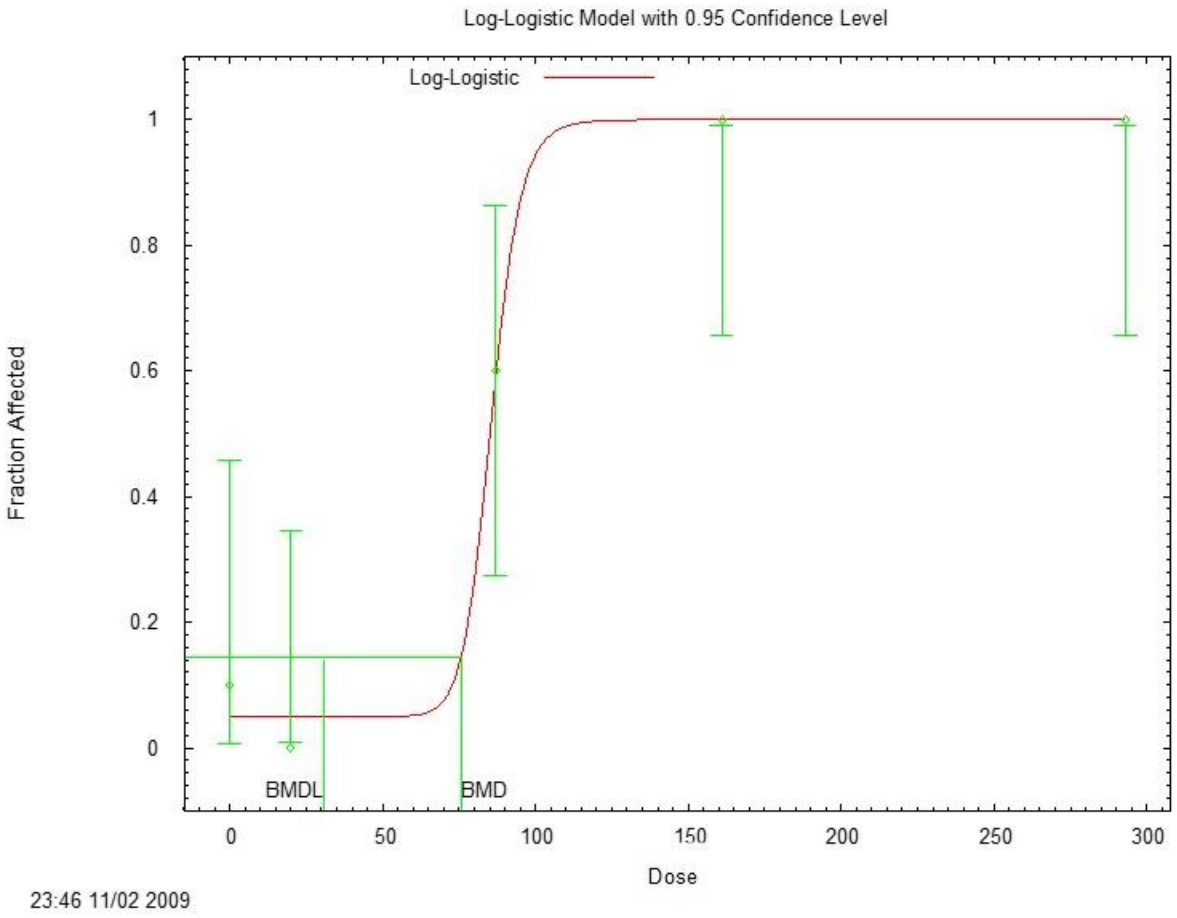
BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (as continuous exposure)

Figure B-1. Fit of Gamma Model to Data on Forestomach Hyperplasia in Male Rats Treated with Ethyl Acrylate in the Drinking Water for 13 Weeks



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (as continuous exposure)

Figure B-2. Fit of Log-logistic Model to Data on Forestomach Hyperplasia in Male Rats Treated with Ethyl Acrylate in the Drinking Water for 13 Weeks



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (as continuous exposure)

Figure B-3. Fit of Log-logistic Model to Data on Forestomach Hyperplasia in Female Rats Treated with Ethyl Acrylate in the Drinking Water for 13 Weeks

APPENDIX C. DETAILS OF BENCHMARK DOSE MODELING FOR CHRONIC p-RfD

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 BMDL is selected as the point of departure when the difference between the BMDLs estimated from these models is more three-fold (unless it is an outlier); otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) is chosen. In accordance with U.S. EPA (2012b) guidance, benchmark doses (BMDs) and lower bounds on the BMD (BMDLs) associated with a BMR of 10% extra risk are calculated for all models.

Model-Fitting Results for Forestomach Hyperkeratosis in Male Rats (NTP, 1986)

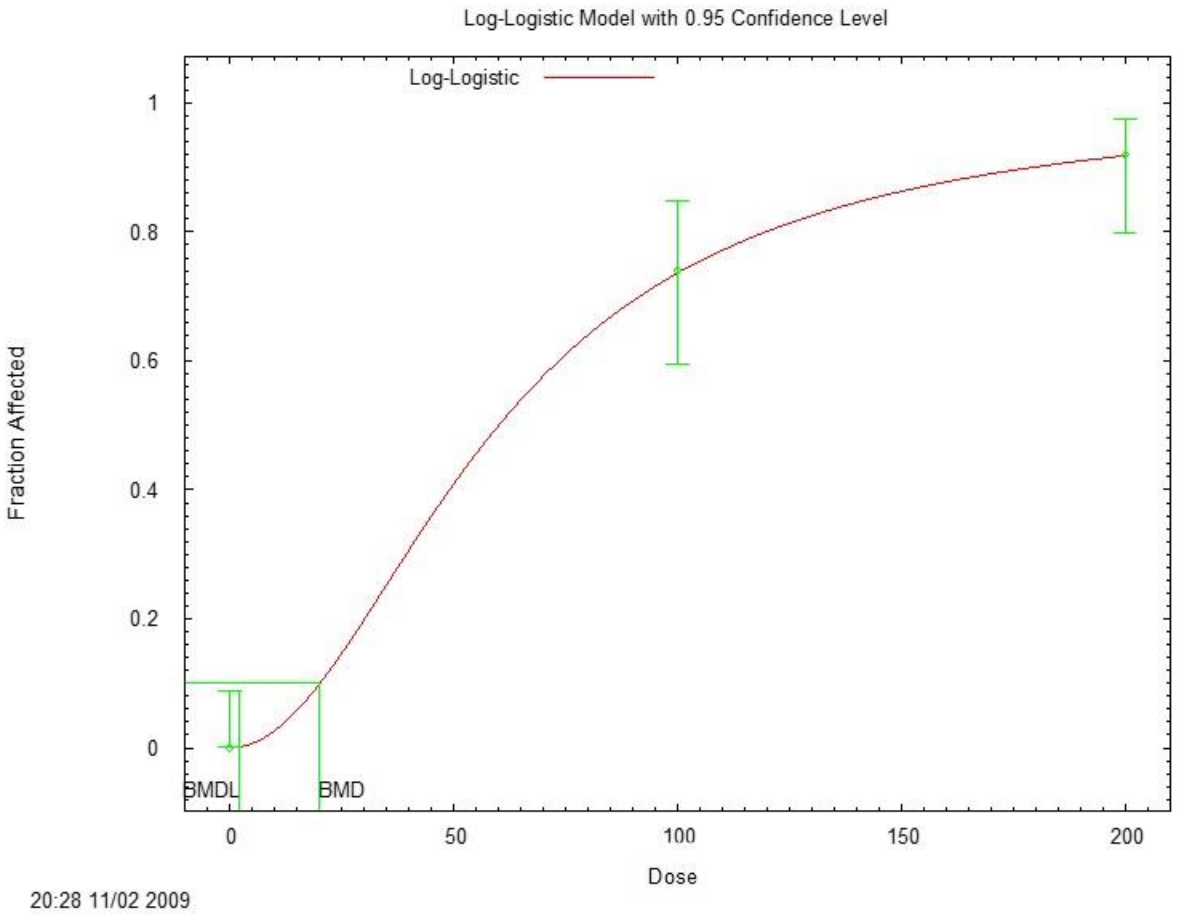
Applying the procedure outlined above to the data (see Table 5) for forestomach hyperkeratosis in male rats exposed chronically to ethyl acrylate via gavage for 103 weeks (NTP, 1986), all but the logistic and probit models provided adequate fit to the data (see Table C-1). The $BMDL_{10}$s from models providing adequate fit differed by more than 3-fold, so the model with the lowest BMDL (log-logistic) was selected. The BMD_{10} and $BMDL_{10}$ for forestomach hyperkeratosis in male rats were 20 and 2.3 mg/kg-day, respectively. Figure C-1 shows the fit of the log-logistic model to the data.

Table C-1. Model Predictions for the Incidence of Forestomach Hyperkeratosis in Male Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	2	0.06	0.97	87.24	8.06	6.52
Logistic	1	13.82	0.00	102.92	32.48	24.05
***Log-Logistic*[c]**	***1***	***0.00***	***1.00***	***89.18***	***19.99***	***2.26***
Log-Probit[c]	1	0.00	1.00	89.18	17.35	11.03
Multistage (degree = 1)[d]	2	0.06	0.97	87.24	8.06	6.52
Multistage (degree = 2)[d]	2	0.06	0.97	87.24	8.06	6.52
Probit	1	14.35	0.00	104.87	30.36	23.18
Weibull[b]	2	0.06	0.97	87.24	8.06	6.52
Quantal-Linear	2	0.06	0.97	87.24	8.06	6.52

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-1. Fit of Log-logistic Model to Data on Forestomach Hyperkeratosis in Male Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model-Fitting Results for Forestomach Hyperplasia in Male Rats (NTP, 1986)

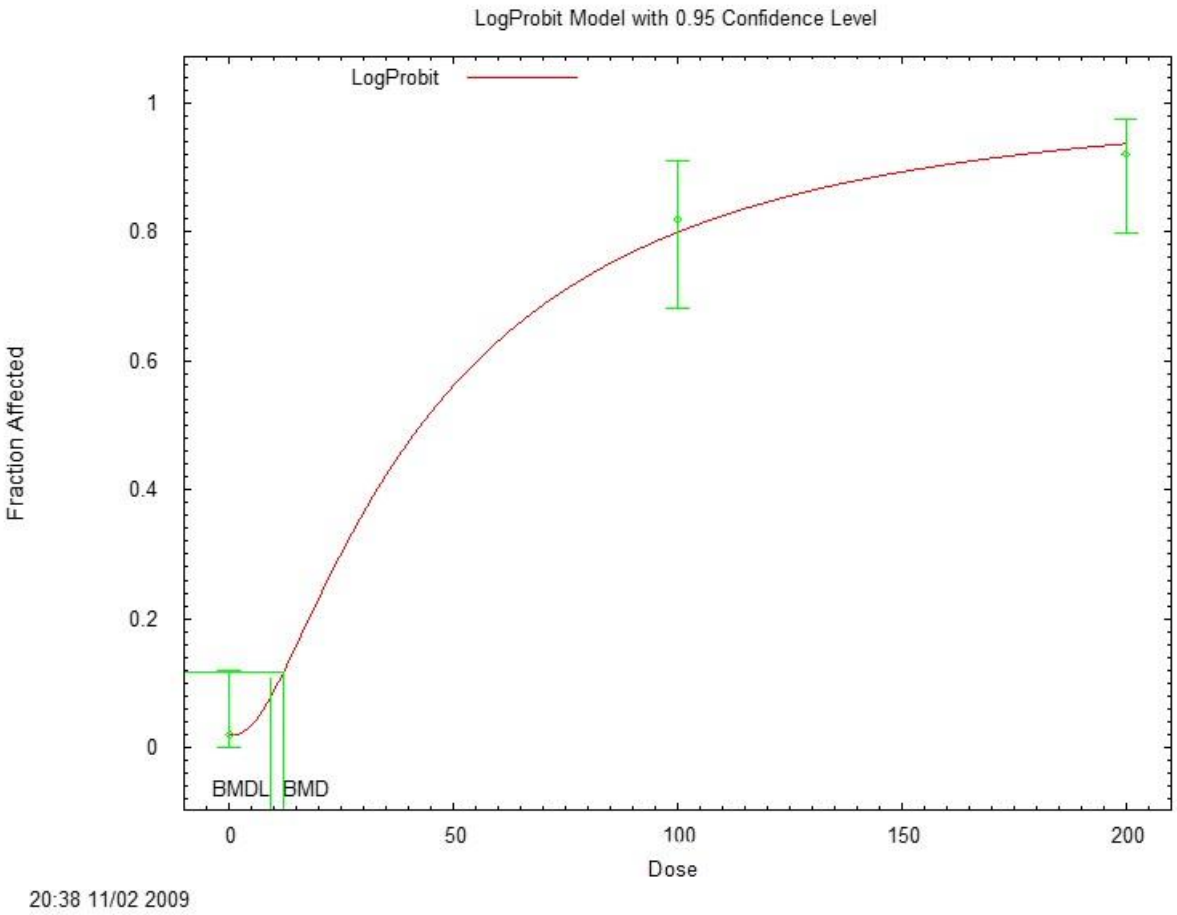
Applying the procedure outlined above to the data (see Table 5) for forestomach hyperplasia in male rats exposed chronically to ethyl acrylate via gavage for 103 weeks (NTP, 1986), all but the logistic, log-logistic, and probit models provided adequate fit to the data (see Table C-2). The $BMDL_{10}$s from models providing adequate fit differed by less than 3-fold, so the model with the lowest AIC (log-probit) was selected. The BMD_{10} and $BMDL_{10}$ for forestomach hyperplasia in male rats were 12 and 9.2 mg/kg-day, respectively. Figure C-2 shows the fit of the log-probit model to the data.

Table C-2. Model Predictions for the Incidence of Forestomach Hyperplasia in Male Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	1	1.39	0.24	90.14	7.18	5.77
Logistic	1	17.99	0.00	102.80	26.38	19.65
Log-Logistic[c]	0	0.00	NA	90.82	6.37	1.38
Log-Probit[c]	***1***	***0.37***	***0.54***	***89.18***	***12.16***	***9.21***
Multistage (degree = 1)[d]	1	1.39	0.24	90.14	7.18	5.77
Multistage (degree = 2)[d]	1	1.39	0.24	90.14	7.18	5.77
Probit	1	18.81	0.00	106.25	24.96	19.46
Weibull[b]	1	1.39	0.24	90.14	7.18	5.77
Quantal-Linear	1	1.39	0.24	90.14	7.18	5.77

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-2. Fit of Log-Probit Model to Data on Forestomach Hyperplasia in Male Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model-Fitting Results for Forestomach Inflammation in Male Rats (NTP, 1986)

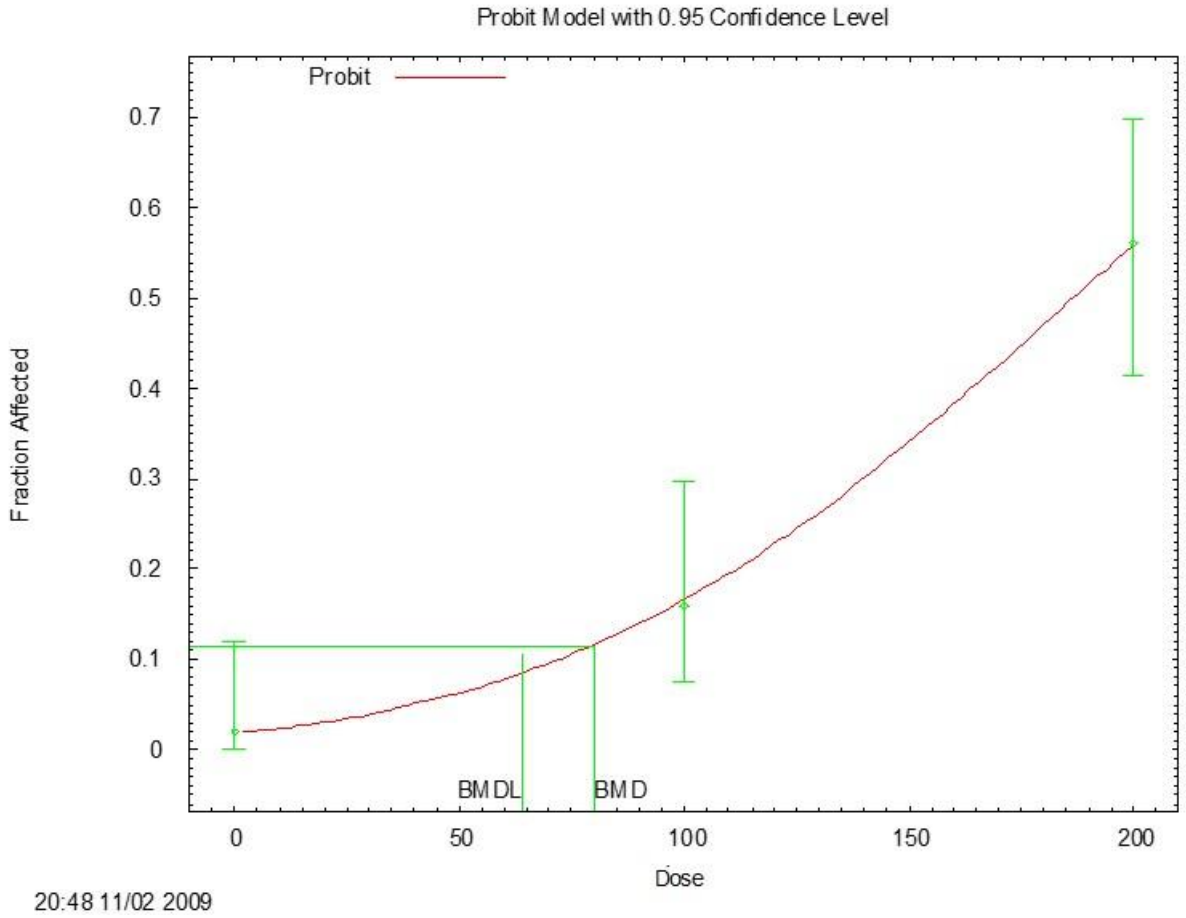
Applying the procedure outlined above to the data (see Table 5) for forestomach inflammation in male rats exposed chronically to ethyl acrylate via gavage for 103 weeks (NTP, 1986), only the logistic, 2-degree multistage, and probit models provided adequate fit to the data (see Table C-3). The $BMDL_{10}$s from models providing adequate fit differed by less than 3-fold, so the model with the lowest AIC (probit) was selected. The BMD_{10} and $BMDL_{10}$ for forestomach inflammation in male rats were 80 and 64 mg/kg-day, respectively. Figure C-3 shows the fit of the probit model to the data.

Table C-3. Model Predictions for the Incidence of Forestomach Inflammation in Male Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0	0.00	NA	128.36	86.85	53.13
Logistic	1	0.07	0.80	126.43	87.10	69.49
Log-Logistic[c]	0	0.00	NA	128.36	86.87	55.73
Log-Probit[c]	0	0.00	NA	128.36	88.34	59.17
Multistage (degree = 1)[d]	1	5.16	0.02	131.89	34.75	26.35
Multistage (degree = 2)[d]	1	0.34	0.56	126.72	74.54	44.55
Probit	***1***	***0.02***	***0.89***	***126.38***	***80.41***	***63.99***
Weibull[b]	0	0.00	NA	128.36	85.21	51.17
Quantal-Linear	1	5.16	0.02	131.89	34.76	26.35

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-3. Fit of Probit Model to Data on Forestomach Inflammation in Male Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model-Fitting Results for Forestomach Hyperkeratosis in Female Rats (NTP, 1986)

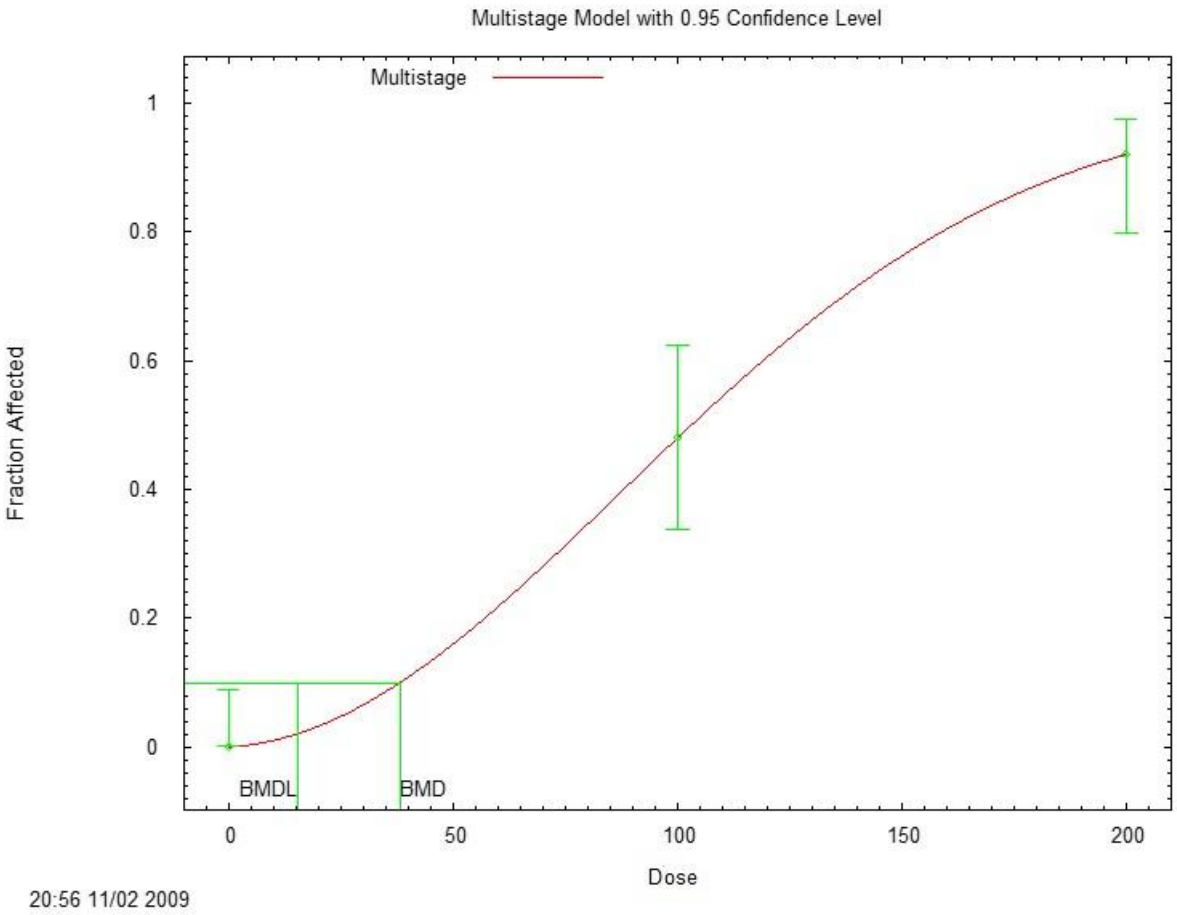
Applying the procedure outlined above to the data (see Table 5) for forestomach hyperkeratosis in female rats exposed chronically to ethyl acrylate via gavage for 103 weeks (NTP, 1986), all but the logistic, 1-degree multistage, and quantal linear models provided adequate fit to the data (see Table C-4). The $BMDL_{10}$s from models providing adequate fit differed by less than 3-fold, so the model with the lowest AIC was examined. The gamma, log-logistic, log-probit, 2-degree multistage, and Weibull models all had the same AIC; the 2-degree multistage model, which resulted in the lowest $BMDL_{10}$ among these, was selected. The BMD_{10} and $BMDL_{10}$ for forestomach hyperkeratosis in female rats were 38 and 15 mg/kg-day, respectively. Figure C-4 shows the fit of the 2-degree multistage model to the data.

Table C-4. Model Predictions for the Incidence of Forestomach Hyperkeratosis in Female Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	1	0.00	1.00	101.11	47.68	23.50
Logistic	1	2.95	0.09	105.36	49.38	37.32
Log-Logistic[c]	1	0.00	1.00	101.11	55.89	35.39
Log-Probit[c]	1	0.00	1.00	101.11	55.63	35.30
Multistage (degree = 1)[d]	2	5.34	0.07	104.87	11.59	9.37
Multistage (degree = 2)[d]	***1***	***0.00***	***1.00***	***101.11***	***38.07***	***15.31***
Probit	1	2.55	0.11	104.66	46.78	35.03
Weibull[b]	1	0.00	1.00	101.11	39.20	20.05
Quantal-Linear	2	5.34	0.07	104.87	11.59	9.37

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-4. Fit of 2-Degree Multistage Model to Data on Forestomach Hyperkeratosis in Female Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model-Fitting Results for Forestomach Hyperplasia in Female Rats (NTP, 1986)

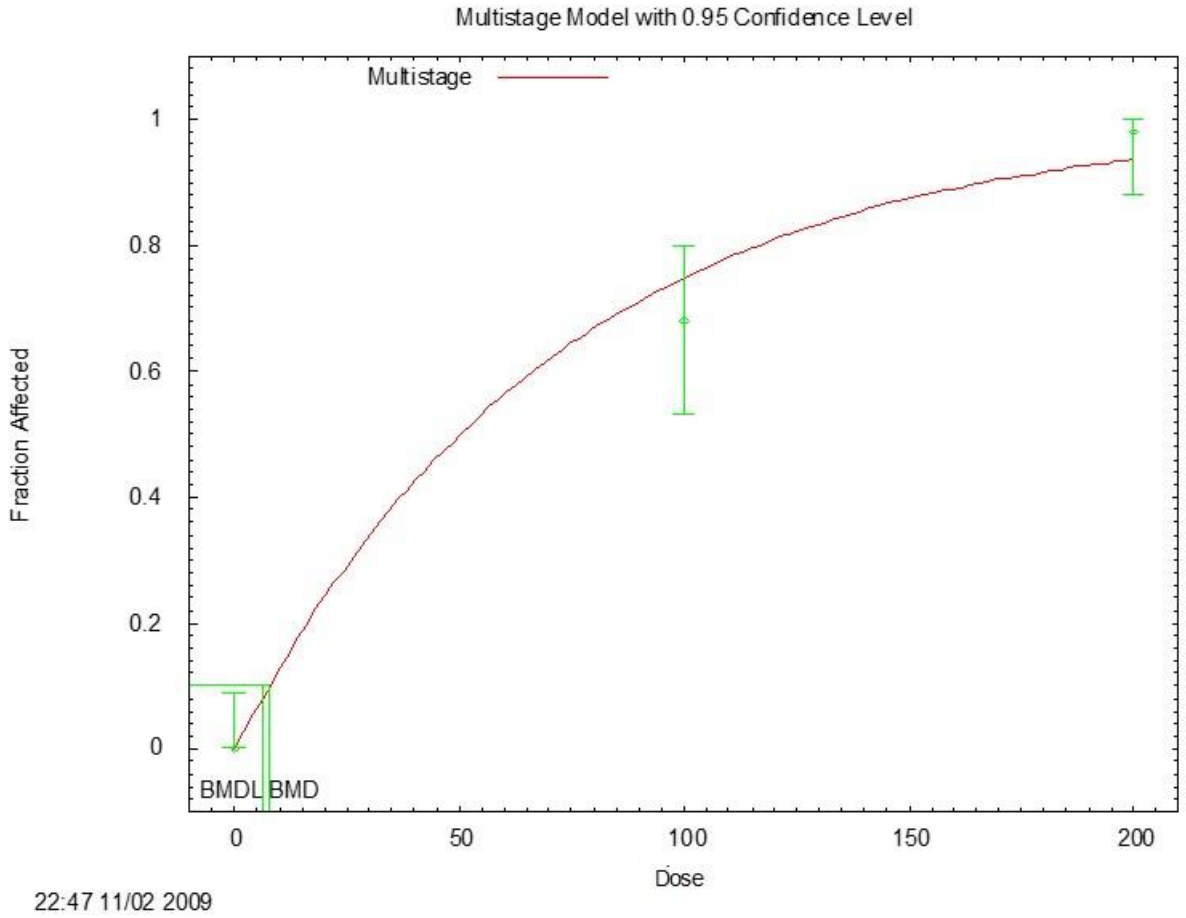
Applying the procedure outlined above to the data (see Table 5) for forestomach hyperplasia in female rats exposed chronically to ethyl acrylate via gavage for 103 weeks (NTP, 1986), all but the logistic and probit models provided adequate fit to the data (see Table C-5). The $BMDL_{10}$s from models providing adequate fit differed by more than 3-fold, so the models with the lowest $BMDL_{10}$ (1-degree multistage, and quantal-linear) were selected. The BMD_{10} and $BMDL_{10}$ for forestomach hyperplasia in female rats were 7.6 and 6.1 mg/kg-day, respectively. Figure C-5 shows the fit of the 1-degree multistage model to the data and Figure C-6 shows the fit of the quantal-linear model to the data.

Table C-5. Model Predictions for the Incidence of Forestomach Hyperplasia in Female Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	1	0.00	1.00	76.49	36.20	10.00
Logistic	1	3.62	0.06	79.68	44.10	30.33
Log-Logistic[c]	1	0.00	1.00	76.49	52.11	27.16
Log-Probit[c]	1	0.00	1.00	76.49	46.56	23.37
Multistage (degree = 1)[d]	***2***	***2.83***	***0.24***	***77.79***	***7.63***	***6.13***
Multistage (degree = 2)[d]	1	0.00	0.99	76.49	21.23	7.86
Probit	1	5.28	0.02	80.99	36.97	26.34
Weibull[b]	1	0.00	1.00	76.49	26.24	9.09
Quantal-Linear	***2***	***2.83***	***0.24***	***77.79***	***7.63***	***6.13***

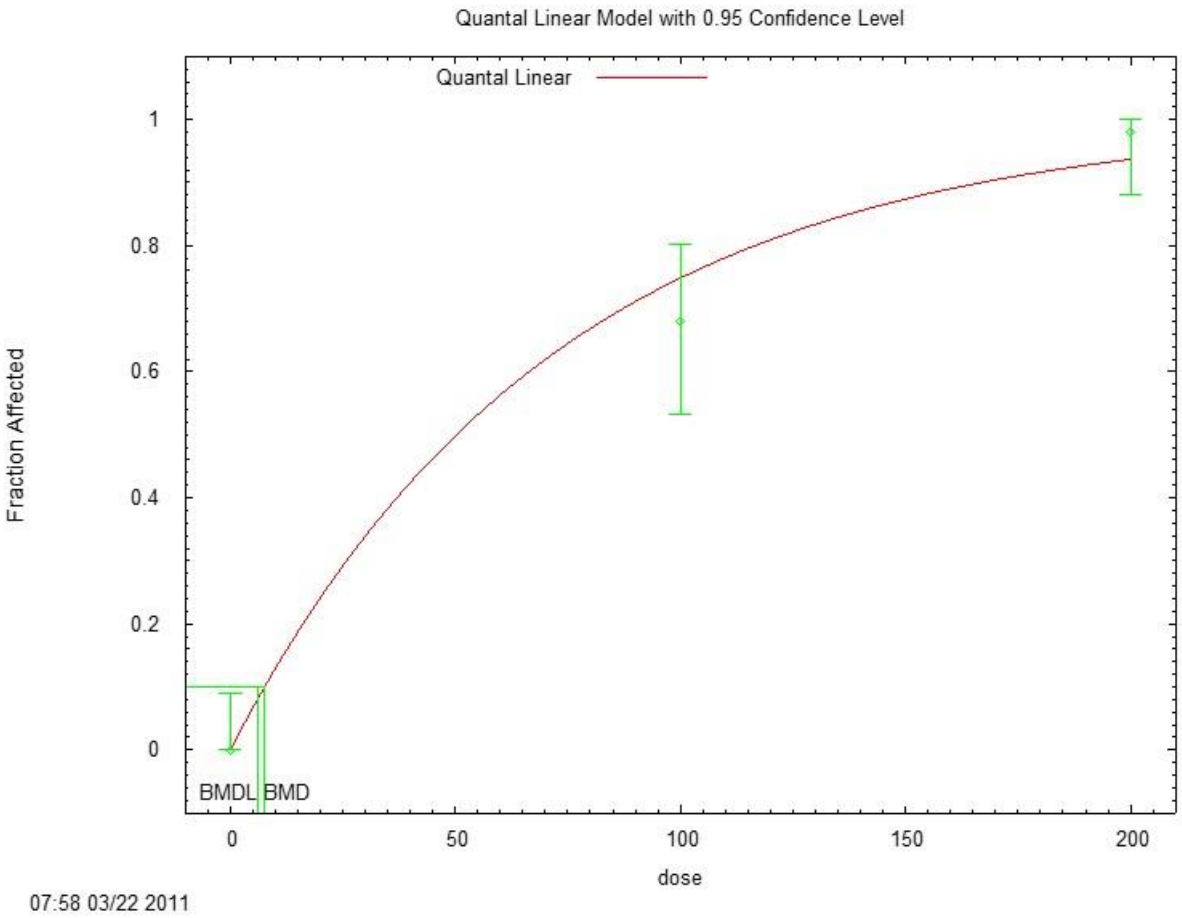
[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-5. Fit of 1-Degree Multistage Model to Data on Forestomach Hyperplasia in Female Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-6. Fit of Quantal-Linear Model to Data on Forestomach Hyperplasia in Female Rats Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model-Fitting Results for Forestomach Hyperkeratosis in Male Mice (NTP, 1986)

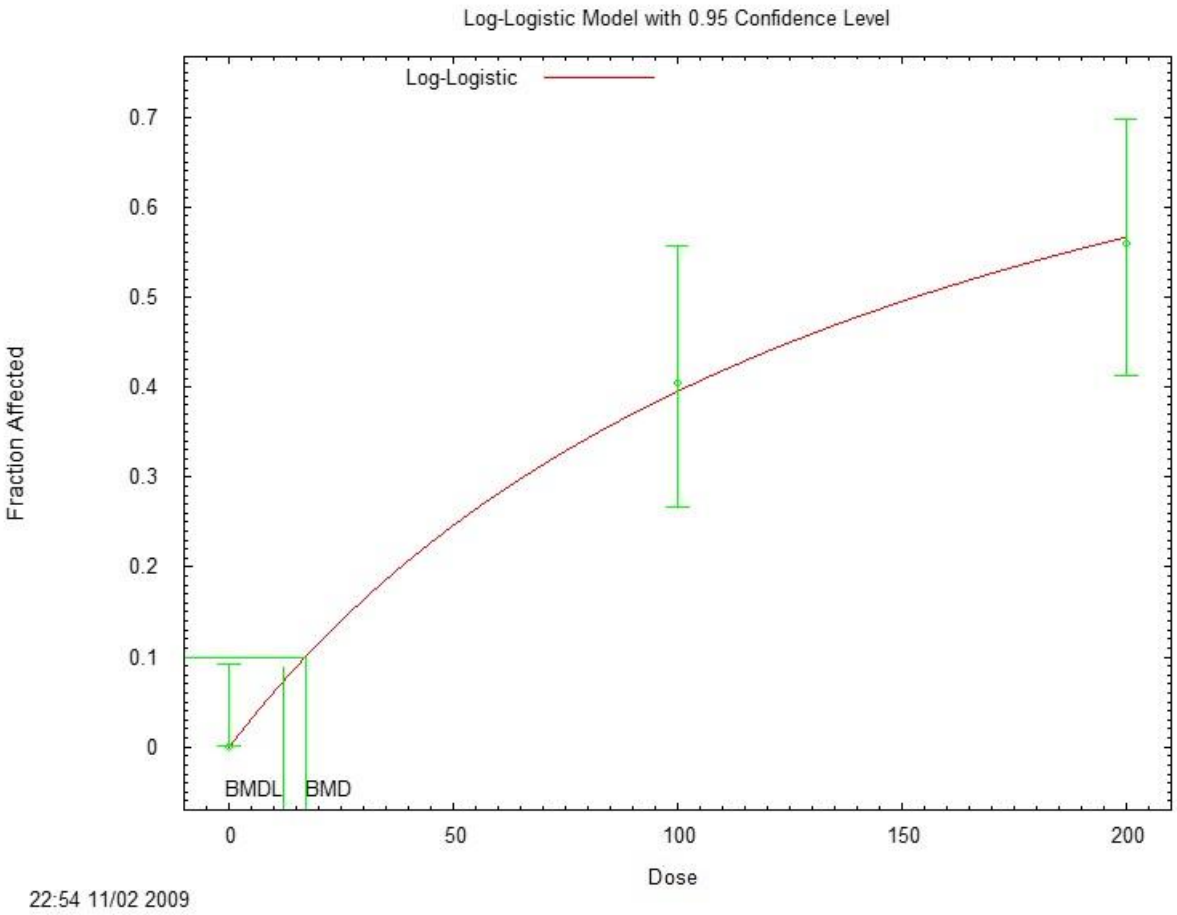
Applying the procedure outlined above to the data (see Table 6) for forestomach hyperkeratosis in male mice exposed chronically to ethyl acrylate via gavage for 103 weeks (NTP, 1986), all but the logistic and probit models provided adequate fit to the data (see Table C-6). The $BMDL_{10}$s from models providing adequate fit differed by less than 3-fold, so the model with the lowest AIC (log-logistic) was selected. The BMD_{10} and $BMDL_{10}$ for forestomach hyperkeratosis in male mice were 17 and 12 mg/kg-day, respectively. Figure C-7 shows the fit of the log-logistic model to the data.

Table C-6. Model Predictions for the Incidence of Forestomach Hyperkeratosis in Male Mice Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	2	0.59	0.75	134.60	23.46	18.51
Logistic	1	9.48	0.00	148.39	61.30	49.33
Log-Logistic[c]	***2***	***0.02***	***0.99***	***134.04***	***16.93***	***12.06***
Log-Probit[c]	2	1.39	0.50	135.37	41.34	33.43
Multistage (degree = 1)[d]	2	0.59	0.75	134.60	23.46	18.51
Multistage (degree = 2)[d]	2	0.59	0.75	134.60	23.46	18.51
Probit	1	8.69	0.00	146.87	58.15	46.95
Weibull[b]	2	0.59	0.75	134.60	23.46	18.51
Quantal-Linear	2	0.59	0.75	134.60	23.46	18.51

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-7. Fit of Log-logistic Model to Data on Forestomach Hyperkeratosis in Male Mice Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model-Fitting Results for Forestomach Hyperplasia in Male Mice (NTP, 1986)

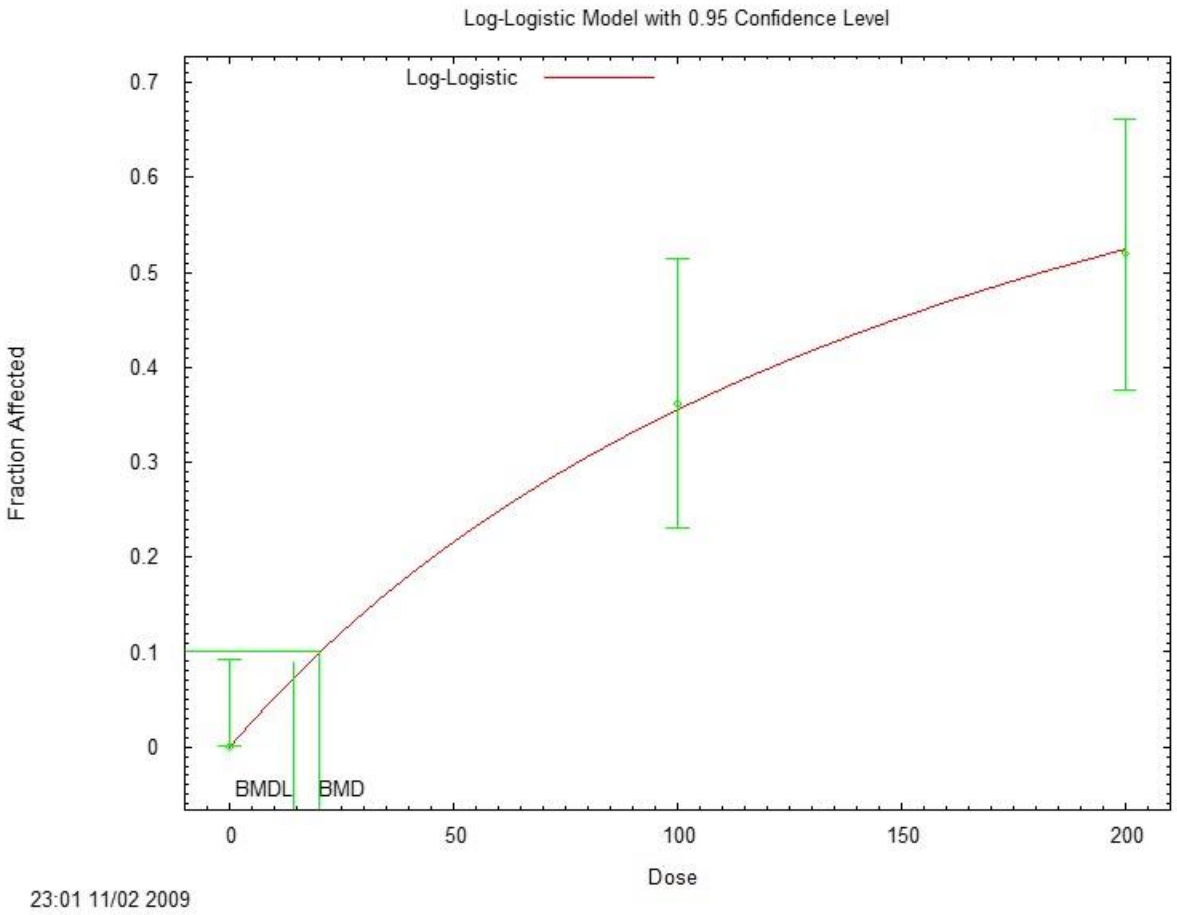
Applying the procedure outlined above to the data (see Table 6) for forestomach hyperplasia in male mice exposed chronically to ethyl acrylate via gavage for 103 weeks (NTP, 1986), all but the logistic and probit models provided adequate fit to the data (see Table C-7). The $BMDL_{10}$s from models providing adequate fit differed by less than 3-fold, so the model with the lowest AIC (log-logistic) was selected. The BMD_{10} and $BMDL_{10}$ for forestomach hyperplasia in male mice were 20 and 14 mg/kg-day, respectively. Figure C-8 shows the fit of the log-logistic model to the data.

Table C-7. Model Predictions for the Incidence of Forestomach Hyperplasia in Male Mice Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	2	0.41	0.82	133.15	26.60	20.80
Logistic	1	8.29	0.00	145.62	67.29	54.26
Log-Logistic[c]	***2***	***0.01***	***0.99***	***132.76***	***20.09***	***14.30***
Log-Probit[c]	2	1.28	0.53	134.00	46.09	37.25
Multistage (degree = 1)[d]	2	0.41	0.82	133.15	26.60	20.80
Multistage (degree = 2)[d]	2	0.41	0.82	133.15	26.60	20.80
Probit	1	7.50	0.01	144.18	63.60	51.38
Weibull[b]	2	0.41	0.82	133.15	26.60	20.80
Quantal-Linear	2	0.41	0.82	133.15	26.60	20.80

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-8. Fit of Log-logistic Model to Data on Forestomach Hyperplasia in Male Mice Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model-Fitting Results for Forestomach Hyperkeratosis in Female Mice (NTP, 1986)

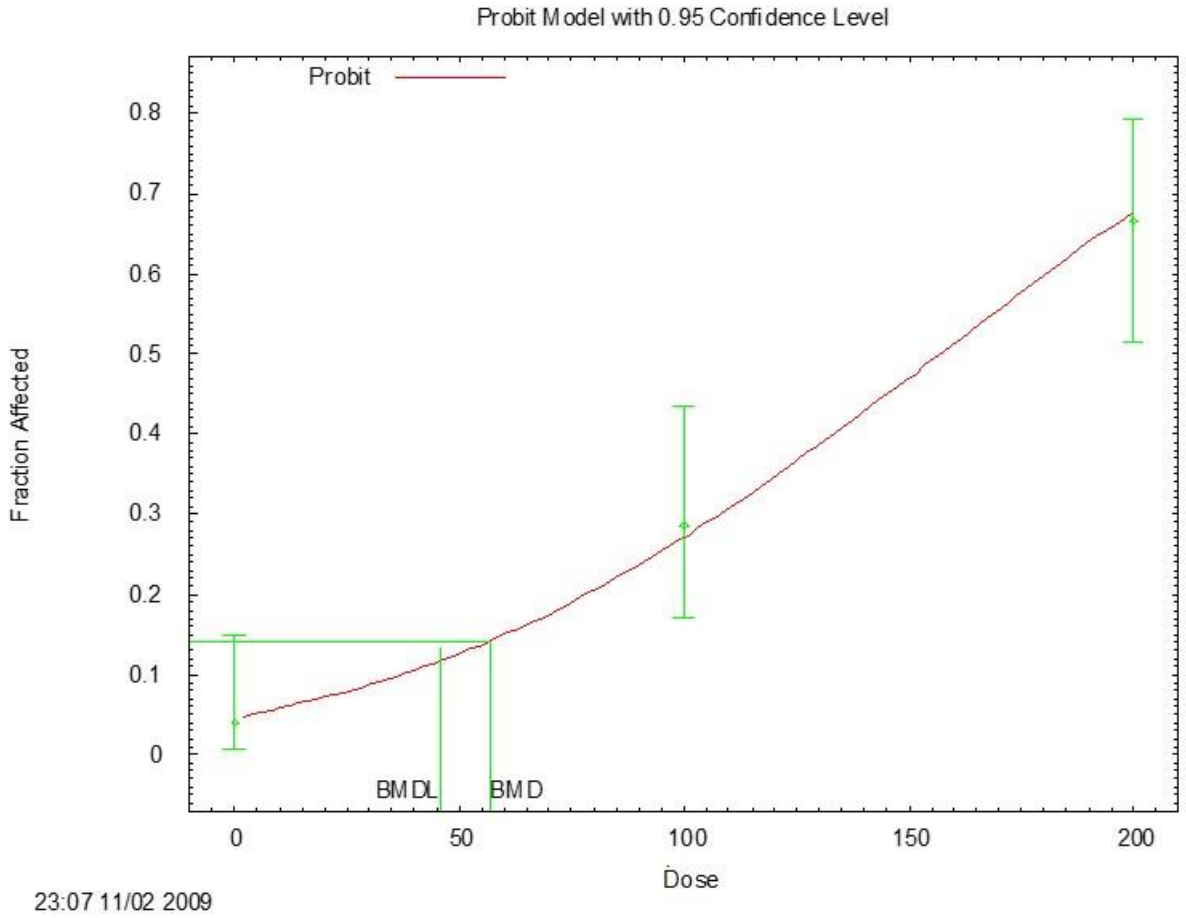
Applying the procedure outlined above to the data (see Table 6) for forestomach hyperkeratosis in female mice exposed chronically to ethyl acrylate via gavage (NTP, 1986), adequate fit to the data was provided only by the logistic, probit, and 1-degree multistage/quantal linear models (see Table C-8). The $BMDL_{10}$s from models providing adequate fit differed by less than 3-fold, so the model with the lowest AIC (probit) was selected. The BMD_{10} and $BMDL_{10}$ for forestomach hyperkeratosis in female mice were 57 and 46 mg/kg-day, respectively. Figure C-9 shows the fit of the probit model to the data.

Table C-8. Model Predictions for the Incidence of Forestomach Hyperkeratosis in Female Mice Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0	0.00	NA	142.53	60.92	24.58
Logistic	1	0.42	0.51	140.97	61.87	49.26
Log-Logistic[c]	0	0.00	NA	142.53	63.05	31.20
Log-Probit[c]	0	0.00	NA	142.53	66.13	38.09
Multistage (degree = 1)[d]	1	2.72	0.10	143.34	24.32	18.83
Multistage (degree = 2)[d]	0	0.00	NA	142.53	55.15	23.57
Probit	***1***	***0.12***	***0.72***	***140.66***	***57.08***	***45.79***
Weibull[b]	0	0.00	NA	142.53	57.06	24.38
Quantal-Linear	1	2.72	0.10	143.34	24.32	18.83

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-9. Fit of Probit Model to Data on Forestomach Hyperkeratosis in Female Mice Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model-Fitting Results for Forestomach Hyperplasia in Female Mice (NTP, 1986)

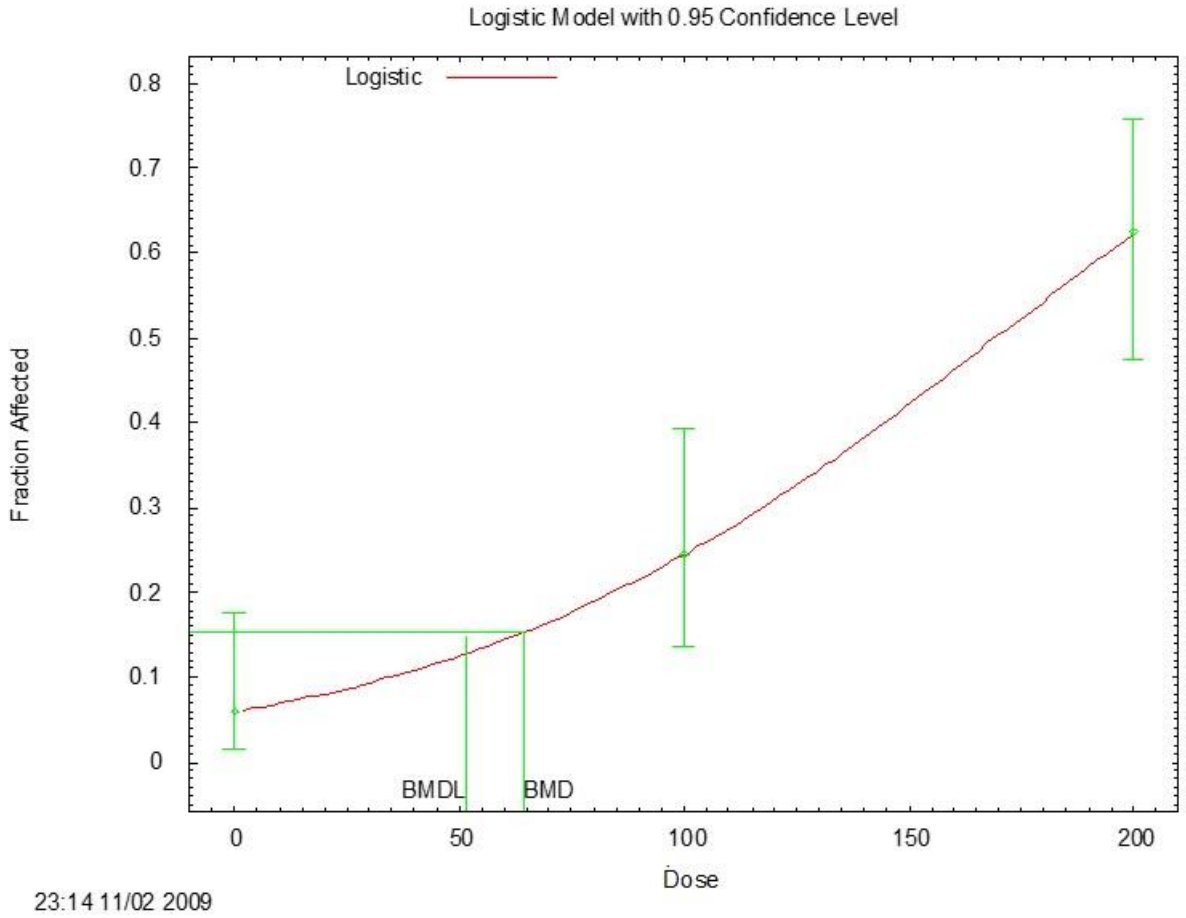
Applying the procedure outlined above to the data (see Table 6) for forestomach hyperplasia in female mice exposed chronically to ethyl acrylate via gavage (NTP, 1986), adequate fit to the data was provided only by the logistic, probit, and 2-degree multistage models (see Table C-9). The $BMDL_{10}$s from models providing adequate fit differed by less than 3-fold, so the model with the lowest AIC (logistic) was selected. The BMD_{10} and $BMDL_{10}$ for forestomach hyperplasia in female mice were 64 and 52 mg/kg-day, respectively. Figure C-10 shows the fit of the logistic model to the data.

Table C-9. Model Predictions for the Incidence of Forestomach Hyperplasia in Female Mice Treated with Ethyl Acrylate by Gavage, for 5 Days/Week, for 103 Weeks

Model	Degrees of Freedom	χ^2	χ^2 Goodness-of-Fit *p*-Value[a]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[b]	0	0.00	NA	146.76	73.22	34.55
Logistic	***1***	***0.00***	***0.99***	***144.76***	***64.35***	***51.71***
Log-Logistic[c]	0	0.00	NA	146.76	73.97	39.60
Log-Probit[c]	0	0.00	NA	146.76	76.53	44.78
Multistage (degree = 1)[d]	1	3.40	0.07	148.30	28.72	21.77
Multistage (degree = 2)[d]	1	0.01	0.91	144.77	68.04	30.73
Probit	1	0.08	0.78	144.84	58.98	47.85
Weibull[b]	0	0.00	NA	146.76	70.21	33.59
Quantal-Linear	1	3.40	0.07	148.30	28.72	21.77

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[b]Power restricted to ≥1.
[c]Slope restricted to ≥1.
[d]Betas restricted to ≥0.

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



BMDs and BMDLs indicated are associated with an extra risk of 10% and are in units of mg/kg-day (5 days/week)

Figure C-10. Fit of Logistic Model to Data on Forestomach Hyperplasia in Female Mice Treated with Ethyl Acrylate by Gavage, for 5 Days/Week for 103 Weeks

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