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Provisional Peer-Reviewed Toxicity Values for

Benzaldehyde
(CASRN 100-52-7)

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 MANAGER

Dan Petersen, PhD, DABT
National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

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

PRIMARY INTERNAL REVIEWERS

Ghazi Dannan, PhD
National Center for Environmental Assessment, Washington, DC

Q. Jay Zhao, PhD, MPH, DABT
National Center for Environmental Assessment, Cincinnati, OH

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
FEV_1	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 BENZALDEHYDE (CASRN 100-52-7)

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.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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

Benzaldehyde, CASRN 100-52-7, occurs naturally in many plants, including cherry, fig, and peach fruit and carnation flowers (Ulker et al., 2013). In some mushrooms, benzaldehyde serves as a natural antibacterial compound (Anderson, 2006). Of 300 different foods evaluated for the presence of benzaldehyde, 150 have been found to contain the compound naturally (Feron et al., 1991). Levels up to 8.9 ppm are found in some fruits. Cinnamon can contain up to 3,000 ppm. Benzaldehyde is a member of the family of "essential oils" in plants, (vanillin, for example, is 4-hydroxy-3-methoxy benzaldehyde), which have antimicrobial and antifeedant properties to discourage parasitism and herbivory. Benzaldehyde is produced by some insects and acts as a chemical defense mechanism or pheromone (Anderson, 2006).

Benzaldehyde is used as a preservative in food, cosmetics, and personal care products (Ulker et al., 2013) and as an intermediate in the manufacture of odorants and flavoring chemicals such as aromatic alcohols (HSDB, 2014). Benzaldehyde is considered to be "generally recognized as safe" (GRAS) for its intended use as a flavor ingredient (Adams et al., 2005), and the Cosmetic Ingredient Review (CIR) Expert Panel concluded that benzaldehyde is safe for use in cosmetic products (Anderson, 2006). Benzaldehyde is also a starting material for various pharmaceuticals, such as ampicillin, and for pesticides, such as dibenzoquat, and is used as a solvent for resins, oils, cellulose acetates, nitrites, and ethers. Benzoic acid and some photographic chemicals are produced using benzaldehyde (HSDB, 2014). Benzaldehyde has been used as a pesticide and bee repellant, but is no longer listed as an active ingredient in any registered pesticide products (HSDB, 2014).

Benzaldehyde is an oily liquid with a high vapor pressure and a moderate measured Henry's law constant. These properties indicate that some volatilization from both dry and moist surfaces is expected to occur (HSDB, 2014). Benzaldehyde is susceptible to degradation by direct photolysis both as a liquid and as a vapor. In addition, benzaldehyde in the atmosphere will react with photochemically generated hydroxyl radicals and has an estimated atmospheric half-life of 30 hours (HSDB, 2014). Benzaldehyde's high water solubility and relatively low estimated soil adsorption coefficient indicate that the chemical, if released into the environment, is likely to leach to groundwater or undergo runoff after a rain event. Thus, removal from soil by leaching with water is expected to compete with volatilization, depending on the local conditions (wet, dry, etc.). The molecular formula for benzaldehyde is C_7H_6O (see Figure 1). Physicochemical properties for benzaldehyde are provided in Table 1.

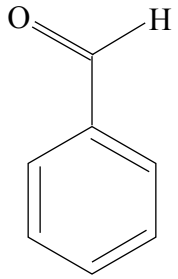

Figure 1. Benzaldehyde Structure

Table 1. Physicochemical Properties for Benzaldehyde (CASRN 100-52-7)[a]

Property (unit)	Value
Physical state	Liquid (almond-scented oil)
Boiling point (°C)	179
Melting point (°C)	−26
Density (g/cm^3 at 15°C)	1.050
Vapor pressure (mm Hg at 25°C)	1.27
pH (unitless)	ND
pKa (unitless)	14.9
Solubility in water (mg/L at 25°C)	6,950
Octanol-water partition constant (log K_{ow})	1.48
Henry's law constant (atm-m^3/mol at 20°C)	2.6×10^{-5}
Soil adsorption coefficient K_{oc} (mL/g)	11.1[b]
Atmospheric OH rate constant (cm^3/molecule-sec at 25°C)	1.29×10^{-11}
Atmospheric half-life (hr)	30
Relative vapor density (air = 1)	3.66
Molecular weight (g/mol)	106.13

[a]HSDB (2014).
[b]U.S. EPA (2012c).

ND = no data.

Literature searches were conducted on sources published from 1900 through September 2015 for studies relevant to the derivation of provisional toxicity values for benzaldehyde (CASRN 100-52-7). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. The following databases were searched: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA OW, U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, OSHA, and RTECS.

A summary of available toxicity values for benzaldehyde from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Benzaldehyde (CASRN 100-52-7)

Source/Parameter[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS (RfD)	1×10^{-1} mg/kg-d	Based on forestomach lesions and kidney toxicity in an oral rat subchronic-duration study	U.S. EPA (1988a)
HEAST (subchronic RfD)	1 mg/kg-d	Based on kidney effects and forestomach lesions in an oral rat study	U.S. EPA (2011a)
HEEP (ADI)	0.214 mg/kg-d	Based on forestomach lesions in an oral rat study	U.S. EPA (1985)
DWSHA	NV	NA	U.S. EPA (2012a)
ATSDR	NV	NA	ATSDR (2015)
WHO (ADI)	0–5 mg/kg BW as benzoic acid equivalents	No safety concern at current levels of intake when used as a flavoring agent	WHO (1967); WHO (2002); JECFA (2003)
Cal/EPA	NV	NA	Cal/EPA (2015a); Cal/EPA (2015b); Cal/EPA (2014)
OSHA	NV	NA	OSHA (2011); OSHA (2006)
NIOSH	NV	NA	NIOSH (2015)
ACGIH	NV	NA	ACGIH (2015)
AIHA (WEEL)	2 ppm (8.7 mg/m^3)	8-hr TWA; established to prevent respiratory and eye irritation from chronic exposure	AIHA (2011); AIHA (1998)
AIHA (WEEL)	4 ppm (17.4 mg/m^3)	STEL, 15 min; established to prevent respiratory and eye irritation from short-term exposure	AIHA (2011); AIHA (1998)
Cancer			
IRIS	NV	NA	U.S. EPA (2015)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012a)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2015a); Cal/EPA (2015b)
ACGIH	NV	NA	ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; AIHA = American Industrial Hygiene Association; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: ADI = acceptable daily intake; RfD = reference dose for chronic oral exposure; STEL = short-term exposure level; TWA = time-weighted average; WEEL = workplace environmental exposure level.

NA = not applicable; NV = not available; BW = body weight.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant database for benzaldehyde and include all potentially relevant and repeated short-term-, subchronic-, and chronic-duration studies. Principal studies are identified. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05 unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for Benzaldehyde (CASRN 100-52-7)								
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[a]**	**Critical Effects**	**NOAEL[a]**	**BMDL/ BMCL[a]**	**LOAEL[a]**	**Reference (comments)**	**Notes[b]**
Human								
1. Oral (mg/kg-d)[a]								
ND								
2. Inhalation (mg/m^3)[a]								
ND								
Animal								
1. Oral (mg/kg-d)[a]								
Short-term[c]	5 M/5 F, F344 rat, gavage in corn oil, 5 d/wk, 16 d	0, 100, 200, 400, 800, 1,600 ADD: 0, 71.4, 143, 286, 571, 1,143	Mortality, reduced body weight in survivors	286	DU	571 (FEL)	NTP (1990); Kluwe et al. (1983)	PR
Short-term[c]	5 M/5 F, B6C3F$_1$ mouse, gavage in corn oil, 5 d/wk, 16 d	0, 200, 400, 800, 1,600, 3,200 ADD: 0, 143, 286, 571, 1,143, 2,286	Mortality	286	DU	1,143 (FEL)	NTP (1990); Kluwe et al. (1983)	PR
Subchronic[d]	**10 M/10 F, F344 rat, gavage in corn oil, 5 d/wk, 13 wk**	**0, 50, 100, 200, 400, 800** **ADD: 0, 36, 71.4, 143, 286, 571**	**M: Mortality; reduced body weight (in survivors); necrotic/degenerative lesions of the brain, liver, and kidney; hyperplasia and hyperkeratosis of the forestomach** **F: Necrotic/degenerative lesions of the brain, liver, and kidney; hyperplasia and hyperkeratosis of the forestomach**	**286**	**DU**	**571 (FEL)**	**NTP (1990); Kluwe et al. (1983)**	**PS, PR, IRIS**

Table 3A. Summary of Potentially Relevant Noncancer Data for Benzaldehyde (CASRN 100-52-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Subchronic[d]	10 M/10 F, B6C3F$_1$ mouse, gavage in corn oil, 5 d/wk, 13 wk	0, 75, 150, 300, 600, 1,200 ADD: 0, 54, 107, 214, 429, 857	M: Mortality, renal tube degeneration of the kidney F: No adverse effects	M: 429 F: 857	DU	M: 857 (FEL) F: ND	NTP (1990); Kluwe et al. (1983)	PR
Subchronic[d]	5–10 M/5–10 F, Osborne-Mendel rat, diet, 16 wk	0, 10,000 ADD: M: 0, 870 ADD: F: 0, 950	No adverse effects	M: 870 F: 950	DU	NDr	Hagan et al. (1967) (Confidence in NOAEL is low because data reporting is inadequate for independent review)	PR
Chronic[e]	50 M/50 F, F344 rat, gavage in corn oil, 5 d/wk, 103 wk	0, 200, 400 ADD: 0, 143, 286	M: Mortality; hyperplasia of the pancreas in males F: No adverse effects	M: 143 F: 286	DU	M: 286 (FEL) F: ND	NTP (1990)	PR
Chronic[e]	50 M/50 F, B6C3F$_1$ mouse, gavage in corn oil, 5 d/wk, M: 104 wk, F: 103 wk	M: 0, 200, 400 F: 0, 300, 600 ADD: M: 0, 143, 286 ADD: F: 0, 214, 429	Hyperplasia of the forestomach	M: 143 F: NDr	NDr	M: 286 F: 214	NTP (1990)	PR
Chronic[e]	5–10 M/5–10 F, Osborne-Mendel rat, diet, 27−28 wk	M: 0, 1,000 F: 0, 1,000 ADD: M: 0, 70 ADD: F: 0, 77	No adverse effects	M: 70 F: 77	DU	NDr	Hagan et al. (1967) (Confidence in NOAEL is low because data reporting is inadequate for independent review.)	PR
Reproductive/ Developmental	ND							

Table 3A. Summary of Potentially Relevant Noncancer Data for Benzaldehyde (CASRN 100-52-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
2. Inhalation (mg/m^3)[a]								
Short-term[c]	14 M/14 F, S-D rat, whole-body inhalation, 6 hr/d, 14 d	0, 500, 750, 1,000 ppm 0, 2,170, 3,260, 4,341 mg/m^3 HEC_{ET}: 0, 87.0, 128, 170[f] HEC_{ER}: 543, 815, and 1,085	Histopathological changes in nasal epithelium, including goblet cell metaplasia in males and mild morphological changes in females	NDr	DU	87	Laham et al. (1991)	PR
Subchronic[d]	ND							
Chronic[e]	ND							
Reproductive/ Developmental	ND							

[a]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to an adjusted daily dose (ADD in mg/kg-day) for oral noncancer effects and a human equivalent concentration (HEC in mg/m^3) for inhalation noncancer effects.
[b]Notes: IRIS = utilized by IRIS; PS = principal study; PR = peer reviewed; NPR = not peer reviewed.
[c]Short-term = repeated exposure for 24 hour to ≤30 days (U.S. EPA, 2002).
[d]Subchronic = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species).
[e]Chronic = repeated exposure for >10% lifespan for humans (more than approximately 90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002).
[f]HEC_{ET} = (ppm × molecular weight ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × $RGDR_{ET}$ (animal:human).

ADD = adjusted daily dose; DU = data unsuitable to BMD modeling; F = female(s); FEL = frank effect level; M = male(s); NA = not applicable; ND = no data; NDr = not determined; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for Benzaldehyde (CASRN 100-52-7)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	BMDL/ BMCL[a]	Reference (comments)	Notes[b]
Human						
1. Oral (mg/kg-d)[a]						
ND						
2. Inhalation (mg/m^3)[a]						
ND						
Animal						
1. Oral (mg/kg-d)[a]						
Carcinogenicity	50 M/50 F, F344 rat, gavage in corn oil, 5 d/wk, 103 wk	0, 200, 400 HED: 0, 34.3, 68.6	No evidence of carcinogenicity	NA	NTP (1990)	PR
Carcinogenicity	**50 M/50 F, B6C3F$_1$ mouse, gavage in corn oil, 5 d/wk, 103–104 wk**	**M: 0, 200, 400 F: 0, 300, 600 HED: M: 0, 20.0, 40.0 HED: F: 0, 30.0, 60.0**	**"Some" evidence of carcinogenicity in both sexes based on significant increases in forestomach papillomas in females, a "near-significant" trend for increased forestomach papillomas in males, and statistically significant increases in preneoplastic forestomach lesions (hyperplasia) in both sexes**	**M: NDr F: 25.7**	**NTP (1990)**	PS, PR
2. Inhalation (mg/m^3)[a]						
ND						

[a]Dosimetry: The units for oral exposures are expressed as HEDs (mg/kg-day). HEDs = dose × (days per week ÷ 7) × species-specific DAFs (based on the animal:human $BW^{1/4}$ ratio recommended by U.S. EPA (2011b), mouse:human ratio = 0.14; rat:human ratio = 0.24)
[b]Notes: PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; HED = human equivalent dose; F = female; M = male; NA = not applicable; ND = no data; NDr = not determined.

HUMAN STUDIES

Oral Exposures

Although no epidemiology studies have examined the effects of benzaldehyde following oral exposure, benzaldehyde is considered a GRAS chemical for use as a food additive for flavoring at levels currently used (IPCS, 2001). There is a single reported case of a person dying after consuming 2 ounces of benzaldehyde (HSDB, 2010).

Inhalation Exposures

The effects of inhalation exposure to benzaldehyde have not been evaluated in humans.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure in animals to benzaldehyde have been evaluated in rats and mice in two short-term-duration (NTP, 1990), three subchronic-duration (NTP, 1990), and three chronic-duration studies (NTP, 1990; Hagan et al., 1967), two of which assessed carcinogenicity (NTP, 1990). Kluwe et al. (1983) provided a preliminary publication of the NTP (1990) short-term- and subchronic-duration data. The NTP (1990) report provides more comprehensive information on study details and results. Some inconsistencies exist between the two publications, which are noted in the study summaries below. For the purposes of this assessment, only data from the NTP (1990) publication are considered.

Short-Term-Duration Studies

NTP (1990); Kluwe et al. (1983) (Rat study)

Groups of F344/N rats (5/sex/group) were administered benzaldehyde (99.5% pure) at doses of 0, 100, 200, 400, 800, or 1,600 mg/kg-day in corn oil via gavage, 5 days/week for a total of 12 doses over a 16-day period. The corresponding adjusted daily doses (ADDs) are 71.4, 143, 286, 571, and 1,143 mg/kg-day, respectively. Animals were examined twice per day for clinical signs of toxicity and weighed on Days 1 and 8, and at study termination. No hematology, clinical chemistry, or urinalysis evaluations were performed. Animals were sacrificed and necropsied at study termination. Microscopic examination of tissues was not performed. The study authors did not conduct statistical analyses of data. However, statistical analyses have been conducted for this review for mortality and body weight data (Fisher's exact test and student's *t*-test; 2-tailed).

All rats administered 1,600 mg/kg-day died on Day 2. In the 800-mg/kg-day group, 2/5 rats of each sex died prior to study termination. No other mortalities were observed (see Table B-1). No clinical signs of toxicity were observed in the surviving rats, according to NTP (1990); however, Kluwe et al. (1983) noted that hyperexcitability, tremors, or inactivity were seen throughout the study in animals of both sexes at 800 and 1,600 mg/kg-day. Mean final body weights in surviving animals in the 800-mg/kg-day group were statistically significantly decreased by 14% in males and 11% in females, compared with controls; body weights in other exposure groups were within 10% of control values (see Table B-1). No gross lesions attributable to benzaldehyde exposure were observed.

A no-observed-adverse-effect level (NOAEL) of 400 mg/kg-day (ADD 286 mg/kg-day) and a lowest-observed-adverse-effect level (LOAEL) (frank effect level [FEL]) of 800 mg/kg-day (ADD 571 mg/kg-day) are identified for increased mortality. Significant decreases in body weight (>10%) were also observed in rats at the FEL.

NTP (1990); Kluwe et al. (1983) (Mouse study)

Groups of $B6C3F_1$ mice (5/sex/group) were administered benzaldehyde (99.5% pure) at doses of 0, 200, 400, 800, 1,600, or 3,200 mg/kg-day in corn oil via gavage, 5 days/week for a total of 12 doses over a 16-day period. The corresponding ADDs are 0, 143, 286, 571, 1,143, and 2,286 mg/kg-day, respectively. Animals were examined twice per day for clinical signs of toxicity and were weighed on Days 1 and 8, and at study termination. No hematology, clinical chemistry, or urinalysis evaluations were performed. Animals were sacrificed and necropsied at study termination. Microscopic examination of tissues was not performed. The study authors did not conduct statistical analyses of data.

All mice administered 1,600 or 3,200 mg/kg-day died by Day 3. In the 800-mg/kg-day group, 1/5 males died on Day 10. No other mortalities were observed. No clinical signs of toxicity were observed during the study. Mean final body weights of the surviving mice were comparable between the exposed and control groups. No gross lesions attributable to benzaldehyde exposure were observed.

A LOAEL (FEL) of 1,600 mg/kg-day (ADD 1,143 mg/kg-day) is identified for increased mortality. The single male death at the next lowest dose, 800 mg/kg-day, may have been chemical related, but due to the low incidence, there is considerable uncertainty, which precludes identifying this dose as either a LOAEL (FEL) or a NOAEL. The next lower dose, 400 mg/kg-day (ADD 286 mg/kg-day), was a clear NOAEL for lack of adverse effects following exposure to benzaldehyde.

Subchronic-Duration Studies

NTP (1990); Kluwe et al. (1983) (Rat study)

In the subchronic study ultimately chosen as the principal study, groups of F344 rats (10/sex/group) were administered benzaldehyde (99.5% pure) at doses of 0, 50, 100, 200, 400, or 800 mg/kg-day in corn oil via gavage, 5 days/week for 13 weeks. The corresponding ADDs are 0, 36, 71.4, 143, 286, and 571 mg/kg-day, respectively. Analytical measurement indicated that dosing formulations were within ±10% of nominal concentrations. Animals were examined twice per day for clinical signs of toxicity. All animals were weighed at study initiation, weekly thereafter, and again at study termination. No hematology, clinical chemistry, or urinalysis evaluations were performed. All animals that died or were sacrificed at study termination were subject to gross necropsy, except for those that were autolyzed or cannibalized. Complete histopathological examinations were conducted on all control animals and animals in the 400- and 800-mg/kg-day groups. Although Kluwe et al. (1983) reported that some organs (i.e., liver, right kidney, thymus, heart, lungs, right testis, and brain) were weighed, the NTP (1990) report does not mention this. Appropriate statistical tests were conducted for lesion incidence data. Statistical analyses have been conducted for this review for mortality and body weight data (Fisher's exact test and student's *t*-test; 2-tailed).

Mortalities observed prior to study termination included 6/10 males and 3/10 females in the 800-mg/kg-day group, 1/10 females in the 400-mg/kg-day group, and 1/10 females in the control group (see Table B-2). The mean final body weight of the four surviving male rats in the 800-mg/kg-day group was significantly decreased by 26% compared with controls; body weights in other exposure groups were within 10% of control values (see Table B-2). No clinical signs of toxicity were reported by NTP (1990); however, Kluwe et al. (1983) reported hyperactivity, trembling, and periodic inactivity in 800-mg/kg-day males and females throughout the study.

Organ weights were not reported by NTP (1990); however, Kluwe et al. (1983) reported marked reductions in absolute and relative-to-brain weights of the thymus and testis in surviving 800-mg/kg-day males, and slight increases in liver, kidney, thymus, and heart weights in surviving 800-mg/kg-day females (quantitative data not provided). Statistically significant increases in the incidences of histopathological lesions were observed in the brain, liver, kidneys, and forestomach of males and females at 800 mg/kg-day compared with controls (see Table B-3). Observed lesions in these rats included minimal to marked brain lesions in all highest-dose rats (degeneration and necrosis of the cerebellum, mineralization of the cerebellum, and/or necrosis of hippocampal neurons), liver and kidney lesions in 30−40% of highest-dose rats (liver and kidney tubule degeneration and/or necrosis), and mild to moderate hyperplasia and/or hyperkeratosis of the forestomach in 50−80% of highest-dose rats. These lesions were not observed in rats administered 400 mg/kg-day (histopathology was not performed at lower doses) according to NTP (1990); however, Kluwe et al. (1983) reported that 2/10 males administered 400 mg/kg-day had forestomach hyperplasia and hyperkeratosis. Kluwe et al. (1983) noted that the significance of the forestomach lesions in animals administered benzaldehyde was unclear, but the presence of these lesions may indicate a mildly irritating effect on the gastric mucosa.

A NOAEL of 400 mg/kg-day (ADD 286 mg/kg-day) and a LOAEL (FEL) of 800 mg/kg-day (ADD 571 mg/kg-day) are identified for increased mortality in males, significantly reduced body weight (>10%) in male survivors, and significant increases in degenerative and necrotic lesions of the brain, liver, and kidney, and hyperplasia and hyperkeratosis of the forestomach in males and females.

NTP (1990); Kluwe et al. (1983) (Mouse study)

Groups of $B6C3F_1$ mice (10/sex/treatment group) were administered benzaldehyde (99.5% pure) at doses of 0, 75, 150, 300, 600, or 1,200 mg/kg-day in corn oil via gavage, 5 days/week for 13 weeks. Analytical measurement indicated that dosing formulations were within ±10% of nominal concentrations. The corresponding ADDs are 0, 54, 107, 214, 429, or 857 mg/kg-day, respectively. Animals were examined twice per day for clinical signs of toxicity. Animals were weighed at study initiation, weekly thereafter, and again at study termination. No hematology, clinical chemistry, or urinalysis evaluations were performed. All animals that died or were sacrificed at study termination were subject to gross necropsy, except for those that were autolyzed or cannibalized. Although Kluwe et al. (1983) reported that some organs (i.e., same organs as those weighed in the 13-week study in rats) were weighed, the NTP (1990) report does not mention this. Organ weights were not reported by NTP (1990); however, Kluwe et al. (1983) indicated that no organ weight changes attributable to exposure were observed. Complete histopathological examinations were conducted on all control and 1,200-mg/kg-day males and females, and on all 600-mg/kg-day males. The kidneys and liver of all 300-mg/kg-day males, and the spleen, stomach, and kidneys of all 600-mg/kg-day females, were also examined. Statistical analyses were reportedly conducted by the study authors, but results were not provided.

Nine of 10 males and 1/10 females administered 1,200 mg/kg-day died during the first week of dosing. The surviving male at 1,200 mg/kg-day died during Week 4. No other mortalities were observed. Terminal body weights of surviving mice were within 10% of control values. No clinical signs of toxicity were observed. The only histopathological lesion attributed to exposure was mild to moderate renal tubule degeneration observed in 1/10 males (but not

statistically significant) in the 600-mg/kg-day group and all (10/10) males in the 1,200-mg/kg-day group.

A NOAEL of 600 mg/kg-day (ADD 428 mg/kg-day) and a LOAEL (FEL) of 1,200 mg/kg-day (ADD 857 mg/kg-day) are identified for increased mortality. Increased incidence of renal tubule degeneration was also observed in males at the FEL.

Hagan et al. (1967)

In a study screening various food flavoring chemicals for adverse effects, groups of Osborne-Mendel rats were administered benzaldehyde (purity not reported) in diet at concentrations of 0 or 10,000 ppm for 16 weeks. Groups exposed to benzaldehyde contained five rats/sex. The control groups contained 10 rats/sex. Using reference values for body weight and food consumption for Osborn-Mendel rats for a subchronic-duration study (U.S. EPA, 1988b), the estimated daily intakes are 870 mg/kg-day in males and 950 mg/kg-day in females. While the study report indicates that diets containing some of the flavorings tested were analyzed to determine the loss of the compound from the diet over a 7-day period, there is no indication that the benzaldehyde diets were tested for benzaldehyde concentration, homogeneity, or stability. Animal body weight, food consumption, and general condition were evaluated weekly. Hematology parameters, including white blood cell (WBC) counts, red blood cell (RBC) counts, hematocrit, and hemoglobin, were measured at study termination. Clinical chemistry and urinalysis evaluations were not performed. At study termination, animals were sacrificed and examined macroscopically. Viscera were removed and the following organs were weighed: liver, kidneys, spleen, heart, and testes. These same organs, as well as the remaining abdominal and thoracic viscera and one hind leg (to provide bone, bone marrow, and muscle), were preserved for histopathological examination from three to four rats/sex in the control and treated groups. The organs examined for histopathological changes were not specified in the study report.

The study authors indicated that no adverse effects attributable to benzaldehyde exposure were observed. No further details were provided. The administered dose of 870 mg/kg-day in males and 950 mg/kg-day in females is an apparent free-standing NOAEL based on a lack of adverse effects. However, confidence in this NOAEL is low because reporting is inadequate for independent review of the findings.

Chronic-Duration/Carcinogenicity Studies

NTP (1990) (Rat study)

Groups of F344 rats (50/sex/treatment group) were administered benzaldehyde (97.8−99.5% pure, with 0.38% benzoic acid and 0.21−0.24% water) at doses of 0, 200, or 400 mg/kg-day in corn oil via gavage, 5 days/week for 103 weeks. Analytical measurements indicated that dosing formulations were within ±10% of target concentrations. The corresponding ADDs are 0, 143, and 286 mg/kg-day, respectively. Animals were examined twice per day for clinical signs of toxicity. Animals were weighed at study initiation, once per week for 13 weeks and then once per month thereafter, and at study termination. No hematology, clinical chemistry, or urinalysis evaluations were performed. At study termination, all animals were sacrificed and subjected to gross necropsy. Complete histopathological examinations were conducted on the controls, low-dose males, high-dose males and females, and all animals that died before study termination. Complete histopathological examinations were conducted on low-dose males because mortality in high-dose males exceeded the control group

by 15%. In low-dose females, only potential target organs were examined microscopically, including adrenal glands, bone, brain, clitoral gland, eyes, gross lesions, heart, kidneys, liver, lungs, pituitary gland, spinal cord, spleen, and stomach.

A significant, dose-related trend was observed for decreased survival in male rats. Using pairwise comparison, survival was significantly decreased in high-dose males (42%) compared to control males (74%) (see Table B-4). Survival in exposed females was comparable to control females. No clinical signs of toxicity were reported, and body weights were similar between exposed and control rats. The only nonneoplastic (preneoplastic) lesion attributed to benzaldehyde exposure was a significant increase in the incidence of pancreatic hyperplasia (nodular masses ≤3 mm in diameter) in high-dose males, compared with controls (see Table B-4). A slight, yet statistically significant, increase in the incidence of adenomas (nodular masses >3 mm in diameter) in the pancreas was also observed in high-dose males; however, the incidence of adenomas was within the historical control incidence range of pancreatic acinar cell neoplasms at the study laboratory, and only slightly above the mean historical control incidence (see Table B-4). Therefore, these tumors were not considered to be treatment-related by the study authors.

There was a statistically significant increase in the incidence of mononuclear cell leukemia (largely due to an increase in Stage 1 leukemia) in the male rats of both treatment groups that showed a statistically significant, dose-related trend (see Table B-4). While the incidence of mononuclear cell leukemia was statistically significantly increased in high-dose males when either the life table test or logistic regression test was used for analysis, the incidence was only statistically significantly increased in the low-dose group when the life table test was used and not when the logistic regression test was used. The study authors considered the logistic regression test to be more appropriate for this analysis due to the relatively large proportion of Stage 1 leukemia. When the incidence of Stages 2 or 3 (combined) leukemia was examined, there was no statistically significant treatment-related increase. Therefore, the study authors did not consider the slight increase in the incidence of leukemia in males to be treatment-related. A statistically significant increase in the incidence of malignant mesotheliomas was noted in low-dose males (see Table B-4); however, this finding was considered to be unrelated to treatment due to the lack of a significant response at the high dose. There were no histopathological lesions in exposed females that were significantly increased relative to controls. The study authors concluded that there was no evidence of carcinogenicity in male or female rats under the conditions of this study.

A NOAEL of 200 mg/kg-day (ADD 143 mg/kg-day) and a LOAEL (FEL) of 400 mg/kg-day (ADD 286 mg/kg-day) are identified in male rats based on decreased survival and increased hyperplasia of the pancreas. A free-standing NOAEL of 400 mg/kg-day is identified for female rats, based on a lack of adverse effects attributable to exposure. There was no clear evidence of carcinogenicity in male or female rats.

NTP (1990) (Mouse study)

Groups of B6C3F$_1$ mice (50/sex/group) were administered benzaldehyde (97.8−99.5% pure, with 0.38% benzoic acid and 0.21−0.24% water) at doses of 0, 200, or 400 mg/kg-day (males) or 0, 300, or 600 mg/kg-day (females) in corn oil via gavage, 5 days/week for 103 (females) or 104 (males) weeks. Analytical measurements indicated that dosing formulations were within ±10% of target concentrations. The corresponding ADDs are 0, 143,

and 286 mg/kg-day for males and 0, 214, and 429 mg/kg-day for females, respectively. Initially, a large number of gavage-associated deaths occurred in the females; therefore, the study with the female mice was restarted. Animals were examined twice per day for clinical signs of toxicity. Animals were weighed at study initiation, once per week for 13 weeks, and then once per month thereafter, and at study termination. No hematology, clinical chemistry, or urinalysis evaluations were performed. All animals were sacrificed and subject to gross necropsy at study termination. Complete histopathological examinations were conducted on the controls, high-dose males and females, and all animals that died before study termination. Histopathological examination of the stomach was also conducted in the low-dose group.

Survival, clinical signs, and body weights were comparable between exposed and control groups. There was a statistically significant increase in the incidence of focal hyperplasia of the forestomach in males in the high-dose group and in females in both treatment groups (see Table B-5). Female mice had a statistically significant increase in the incidence of squamous cell papillomas of the forestomach at both doses with a statistically significant, dose-dependent trend. There was also a slight, but not statistically significant, increase in the incidence of squamous cell papillomas of the forestomach in male mice of the high-dose group that was above the historical control incidence (see Table B-5). The study authors concluded that there was some evidence of carcinogenic activity of benzaldehyde in male and female mice, based on the increased incidences of neoplastic and preneoplastic lesions of the forestomach.

In males, a NOAEL of 200 mg/kg-day (ADD 143 mg/kg-day) and a LOAEL of 400 mg/kg-day (ADD 286 mg/kg-day) are identified for increased incidence of forestomach hyperplasia. In females, a LOAEL of 300 mg/kg-day (ADD 214 mg/kg-day), with no NOAEL, was identified for increased incidence of forestomach hyperplasia. There was some evidence of carcinogenicity under the conditions of this study based on an increase in the incidence squamous cell papilloma and hyperplasia of the forestomach.

Hagan et al. (1967)

In a study screening various food flavoring chemicals for adverse effects, groups of Osborne-Mendel rats were administered dietary benzaldehyde (purity not reported) at concentrations of 0 or 1,000 ppm for 27−28 weeks. Groups exposed to benzaldehyde contained five rats/sex. The control groups contained 10 rats/sex. Using reference values for body weight and food consumption for Osborn-Mendel rats in a chronic-duration study (U.S. EPA, 1988b), the estimated daily intakes are 70 mg/kg-day in males and 77 mg/kg-day in females. Study design and endpoints evaluated are identical to those described above for the 16-week study by the same authors.

The study authors indicated that no adverse effects attributable to benzaldehyde exposure were observed. No further details were provided. The administered dose of 70 mg/kg-day (ADD 70 mg/kg-day) in males and 77 mg/kg-day (ADD 77 mg/kg-day) in females is an apparent free-standing NOAEL based on a lack of adverse effects. However, confidence in this NOAEL is low because reporting is inadequate for independent review of the findings.

Reproductive/Developmental Studies

No studies have been identified.

Inhalation Exposures

The effects of inhalation exposure in animals to benzaldehyde have been evaluated in one short-term-duration study (Laham et al., 1991).

Laham et al. (1991)

Groups of Sprague-Dawley (S-D) rats (14/sex/group) were exposed to benzaldehyde (≥98% pure) at concentrations of 0, 500, 750, or 1,000 ppm via whole-body inhalation for 6 hours/day for 14 consecutive days. These concentrations are equivalent to 0, 2,170, 3,260, and 4,341 mg/m^3, respectively. Control groups were exposed to filtered air, and kept in a separate room to avoid contamination from animals in the benzaldehyde-treatment groups. The exposure concentrations were selected based on a range-finding test that indicated zero mortality in the same rat strain after one 6-hour exposure at concentrations up to 1,000 ppm (4,341 mg/m^3). During the 14-day study, chamber concentrations were determined every 6 minutes in each chamber; however, analytically determined concentrations were not provided in the study report. Animals were examined daily for clinical signs of toxicity. Animals were weighed after 2, 8, and 14 exposures. Rectal temperatures were obtained within 30 minutes after 2, 7, and 14 exposures, and 20 hours after the last exposure. Blood was collected at necropsy from 4−6 rats/group for hematology (hematocrit [Hct], hemoglobin [Hb], erythrocyte count [RBC], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], total leucocyte count [WBC], and acetylcholinesterase [AChE] in RBCs) and clinical chemistry (blood urea nitrogen [BUN], total protein, albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ-glutamyl transferase [GGT], alkaline phosphatase [ALP], lactate dehydrogenase, creatine phosphokinase, alpha-hydroxybutyrate dehydrogenase, cholinesterase, bilirubin, cholesterol, glucose, inorganic phosphorus, triglycerides, calcium, chloride, magnesium, potassium, sodium, and amylase). Urinalysis evaluations were not performed.

As available in surviving animals, seven rats/sex/group were sacrificed and necropsied 72 hours after the last exposure. The remaining animals were whole-body perfused and prepared for future examination with an electron microscope. The brain, heart, kidneys, liver, lungs, and spleen were collected and weighed at terminal sacrifice prior to fixation for histology examination. Other tissues that were histologically examined included the adrenal glands, small and large intestines, larynx, rhinopharynx, stomach, trachea, testes or ovaries, thyroid, and urinary bladder. The nasal tissues from rats in the control, low-dose, and high-dose groups were decalcified and processed for histology, with special attention paid to the respiratory, olfactory, and stratified squamous epithelia. Animals that were found moribund were immediately necropsied and tissues were examined microscopically. The study authors performed appropriate statistical tests.

Mortalities during the first week of exposure included 10/14 females and 1/14 males exposed to 4,341 mg/m^3 and 1/14 females exposed to 3,260 mg/m^3. During the second week, two additional females exposed to 3,260 mg/m^3 were found dead or were sacrificed due to morbidity. Rats exposed to 4,341 mg/m^3 showed several clinical signs of toxicity following exposure, including aggression and tremors when handled, extreme sensitivity to noise, abnormal gait, frequent seizures, positive Straub sign, piloerection, diuresis, and reduced breathing rate. There were signs of nasal and ocular irritation that appeared to be concentration related, but the specifics were not reported. Formation of excessive amounts of porphyrin pigments was noted around eyes and nares, primarily in animals exposed to 4,341 mg/m^3. All benzaldehyde-treated

groups showed a slight (≤6%), but statistically significant, decrease in mean body temperature after 2, 7, and 14 exposures; body temperatures returned to normal within 20 hours after the cessation of exposure. A statistically significant decrease in terminal body weight was reported in all male groups; however, mean body weights were within 10% of the control mean for all groups (see Table B-6). Mean body weights of females were unaffected by exposure.

Several changes in hematology and clinical chemistry parameters were noted in exposed rats, relative to controls (see Tables B-7 and B-8). Statistically significant changes in RBC parameters were minimal (≤13% different from control), including decreased hemoglobin and hematocrit in males and females at 4,341 mg/m^3, decreased RBCs in females at 4,341 mg/m^3, and decreased MCH and MCHC in males at ≥3,260 mg/m^3. Significant changes in WBCs included a significant 7–10-fold increase in monocytes at ≥2,170 mg/m^3 in females and a 35% increase in WBC count at 4,341 mg/m^3 in males. For clinical chemistry, significant increases in serum AST levels (31−152%) were observed in males and females from all exposure groups. Other significant clinical chemistry changes were observed in females from all exposure groups, compared to controls, including an 8–11% decrease in serum albumin, a 5−7% decrease in serum total protein, and a 26–35% decrease in serum cholinesterase levels. Serum ALT was significantly elevated by 34% at 3,260 mg/m^3 in females, but not at 4,341 mg/m^3. Both absolute and relative liver weights were significantly elevated in all exposed female groups; however, the increase was greatest at 2,170 mg/m^3 (30−31%) and lowest at 4,341 mg/m^3 (15%) (see Table B-6). In males, a significant 18% increase in relative liver weight was reported at 2,170 mg/mg^3. No other organ weight changes were reported in exposed animals compared with controls (data not provided).

Serum chemistry findings and liver weight changes were not accompanied by histopathological changes. The only specific histopathological change attributed to benzaldehyde exposure was goblet cell metaplasia, mainly in the respiratory epithelium lining of the nasal septum. This finding was noted in 4/7 males at both 2,170 and 4,341 mg/m^3 (the 3,260-mg/m^3 group was not examined) with no differences in severity between the groups. In females, 1/7 control animals had slight goblet cell metaplasia, while 3/7 in the 2,170-mg/m^3 group and 1/7 in the 4,341-mg/m^3 group (the 3,260-mg/m^3 group was not examined) had "mild morphological changes" in the nasal tissues. However, due to the large number of female deaths at 4,340 mg/m^3 during the first week of exposure (10/14), only four females in this group (4/14) were exposed to benzaldehyde for 14 days. The study authors indicated no other signs of inflammation or alterations in the nasal tissues.

A LOAEL of 2,170 mg/m^3 (HEC_{ET} 87.0 mg/m^3) is identified in exposed rats based on histopathological changes in the nasal tissue (extrathoracic region), including goblet cell metaplasia in males and mild morphological changes in females. Evidence for liver effects in females was also observed at the LOAEL, including increased liver weight accompanied by clinical chemistry changes in females; however, no morphological changes were observed in the liver. No NOAEL is identified. For effects in the extrathoracic (ET) region of rat respiratory tract, nominal inhalation concentrations of 500, 750, and 1,000 ppm (2,170, 3,260, and 4,341 mg/m^3) have been converted to human equivalent concentrations (HEC_{ETS}) of 87.0, 128, and 170 mg/m^3, respectively, by treating benzaldehyde as a Category 1 gas and using the following equation (U.S. EPA, 1994):

HEC_{ET} = (ppm × MW ÷ 24.45)
× (hours/day exposed ÷ 24)
× (days/week exposed ÷ 7) × $RGDR_{ET}$

where:

MW = molecular weight
$RGDR_{ET}$ = extrathoracic regional gas dose ratio
= RGD_{rat}/RGD_{human}

Extrathoracic regional gas doses (RGD) have been calculated as follows:

RGD = $V_E \div SA_{ET}$

where:

V_E = minute volume
= 171 mL/minute in rats and 13,800 mL/minute in humans
SA_{ET} = surface area of the extrathoracic region
= 15 cm^2 in rats and 200 cm^2 in humans

As inhaled benzaldehyde was also associated with extrarespiratory (ER) effects in the liver, nominal concentrations of 500, 750, and 1,000 ppm (2,170, 3,260, and 4,341 mg/m^3) were converted to HEC_{ER}s of 543, 815, and 1,085 mg/m^3, respectively, by treating benzaldehyde as a Category 3 gas and using the following equation (U.S. EPA, 1994):

HEC_{ER} = (ppm × MW ÷ 24.45)
× (hours/day exposed ÷ 24)
× (days/week exposed ÷ 7)
× ratio of blood:gas partition coefficient (animal:human)

where:

MW = molecular weight

The value for the rat blood:air partition coefficient for benzaldehyde is greater than the human blood:air partition coefficient, so the default ratio of 1 was applied.

Subchronic-Duration Studies
No studies have been identified.

Chronic-Duration/Carcinogenicity Studies
No studies have been identified.

Reproductive/Developmental Studies
No studies have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)
Genotoxicity Studies

The potential genotoxicity of benzaldehyde has been evaluated in numerous in vitro studies; no in vivo mammalian studies have been located. Available studies are summarized below (see Table 4A for more details). In general, available data indicate that benzaldehyde is not mutagenic, but evidence indicates that benzaldehyde may cause deoxyribonucleic acid (DNA) damage and clastogenic effects.

The vast majority of mutagenicity studies indicate that benzaldehyde is not mutagenic in vitro. All available studies using traditional *Salmonella typhimurium* tester strains indicate that benzaldehyde is not mutagenic with or without metabolic activation (Dillon et al., 1998; Gee et al., 1998; Tennant and Ashby, 1991; NTP, 1990; Vamvakas et al., 1989; Nohmi et al., 1985; Haworth et al., 1983; Kasamaki et al., 1982; Florin et al., 1980; Rapson et al., 1980; Rockwell and Raw, 1979; Sasaki and Endo, 1978). Using base-specific tester strains TA7001, TA7002, TA7003, TA7004, TA7005, and TA7006 both with and without metabolic activation, Gee et al. (1998) reported mutagenicity only in TA7005 with metabolic activation (TA7005 specifically detects G:C → A:T mutations). In L5178Y TK ± mouse lymphoma cells, one study reported mutations at near-cytotoxic concentrations (Mcgregor et al., 1991; NTP, 1990), while another did not observe mutagenicity at similar doses (Microbiological Associates, 1991). Benzaldehyde did not cause sex-linked recessive lethal mutations in *Drosophila melanogaster* (NTP, 1990; Woodruff et al., 1985).

A limited number of studies indicate that benzaldehyde is clastogenic in vitro. Benzaldehyde induced chromosomal aberrations (CAs) in Chinese hamster lung cells without metabolic activation (but not with metabolic activation) and in Chinese hamster B241 cells (metabolic conditions unknown) (Sofuni et al., 1985; Kasamaki et al., 1982); however, CAs were not induced in Chinese hamster ovary (CHO) cells with or without activation (NTP, 1990; Galloway et al., 1987). Sister chromatid exchanges (SCEs) were observed in CHO cells and human lymphocytes exposed to benzaldehyde without metabolic activation; induction was equivocal in CHO cells with metabolic activation (NTP, 1990; Jansson et al., 1988; Galloway et al., 1987).

The evidence indicates that benzaldehyde may cause DNA damage, but is not conclusive. In the *Bacillus subtilis* rec assay, benzaldehyde showed equivocal evidence of DNA damage in one study (Matsui et al., 1989) and no evidence of DNA damage in a second study [Oda et al. (1978) as cited in Adams et al. (2005)]. Using the comet assay, dose-dependent DNA damage was observed in *D. melanogaster* larvae exposed to benzaldehyde (Demir and Kaya, 2013). In human cells exposed to benzaldehyde in vitro, DNA damage was significantly increased in human lymphocytes (Demir et al., 2010) and DNA protein cross-links were formed in human Burkitt lymphoma cells (Kuykendall et al., 2007). However, DNA cleavage was not observed in extracellular purified supercoiled DNA (PM2 bacteriophage) exposed to benzaldehyde (Becker et al., 1996).

Table 4A. Summary of Benzaldehyde Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results[a]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Mutation	*S. typhimurium* TA98, TA1537 (traditional tester strains) *S. typhimurium* TA7001, TA7002, TA7003, TA7004, TA7005, TA7006 (base-specific tester strains); individually and as a mix	50–1,000 µg/mL	−	+ TA7005 − TA98, TA1537, TA7001, TA7002, TA7003, TA7004, TA7006, and mixture	The liquid fluctuation test method was used. The concentration at which the number of revertants was increased in TA7005 with metabolic activation was not reported. TA7005 detects G:C → A:T mutations.	Gee et al. (1998)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	0, 10, 33, 100, 333, 1,000 µg/plate	−	−	Cytotoxicity was observed at 1,000 µg/plate.	Tennant and Ashby (1991); NTP (1990); Haworth et al. (1983)
Mutation	*S. typhimurium* TA100, TA102, TA104	0, 33, 100, 333, 1,000, 3,333 µg/plate	−	−	Cytotoxicity was observed at 3,333 µg/plate.	Dillon et al. (1998); Tennant and Ashby (1991); NTP (1990)
Mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	3 µmol	−	−		Florin et al. (1980)
Mutation	*S. typhimurium* TA98, TA100, TA2637	0, 50, 100, 200, 500, 1,000, 2,000 µg/plate	−	−	Article was published in a Japanese language journal, but the abstract and tables are in English.	Nohmi et al. (1985)
Mutation	*S. typhimurium* TA98, TA100	0.05–500 µg/plate	−	−		Kasamaki et al. (1982)
Mutation	*S. typhimurium* TA98, TA100	0.05–100 µL/plate	ND	−		Rockwell and Raw (1979)

Table 4A. Summary of Benzaldehyde Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results[a]		Comments	References
			Without Activation	With Activation		
Mutation	*S. typhimurium* TA98, TA100	50–300 µL/plate	ND	−	Plates were treated with 24-hr urine from benzaldehyde-treated rats in the presence of S9; amount administered to rats was not reported.	Rockwell and Raw (1979)
Mutation	*S. typhimurium* TA98, TA100	NR	−	−		Sasaki and Endo (1978) [abstract only]
Mutation	*S. typhimurium* TA100	0.1, 1, 10, 100, 1,000 µg/plate	−	ND		Rapson et al. (1980)
Mutation	*S. typhimurium* TA100	0.1–2,000 nmol/plate	−	−		Vamvakas et al. (1989)
DNA damage (rec-assay)	*B. subtilis* strains H17 ($recE^+$) and M45 ($recE^-$)	2,000 mg/L	−	±	Based on S-probit analysis, benzaldehyde had DNA-damaging potential. However, repaired survival analyses did not indicate DNA damage; 2,000 mg/L was the highest concentration of benzaldehyde giving 50% survival turbidity of the $recE^{\pm}$ strains (the other concentrations of benzaldehyde tested not reported).	Matsui et al. (1989)
DNA damage (rec-assay)	*B. subtilis* strains H17 ($recE^+$) and M45 ($recE^-$)	21 µg/plate	−	ND	Japanese article with English summary.	Oda et al. (1978) as cited in Adams et al. (2005)
Genotoxicity studies in nonmammalian eukaryotic organisms						
Sex-linked recessive lethal mutation	Canton-S wild-type *D. melanogaster* (adult males); feeding or injection exposure	Feeding: 0, 1,150 ppm Injection 0, 2,500 ppm	−	NA	No induction of sex-linked recessive lethal mutations was observed via either route.	NTP (1990); Woodruff et al. (1985)

Table 4A. Summary of Benzaldehyde Genotoxicity						
Endpoint	**Test System**	**Dose/ Concentration**	**Results[a]**		**Comments**	**References**
			Without Activation	**With Activation**		
DNA damage (comet assay)	Hemocytes from *D. melanogaster*, 72-hr-old larvae (third instar); feeding exposure	0, 5, 10, 25, 50 mM	+	NA	Dose-dependent increases in DNA damage were observed at concentrations ≥10 mM, based on statistically significant ($p < 0.05$) increases in % DNA tail (≥10 mM), tail moment (≥10 mM), and tail length (≥25 mM) assay parameters.	Demir and Kaya (2013)
Genotoxicity studies in mammalian cells—in vitro						
Mutation	L5178Y TK ± mouse lymphoma cells	0, 100, 200, 300, 400, 450, 475, 500, 525, 550, 575, 600, 625, 650 µg/mL	−	ND	Mutagenesis was not observed at doses that did not cause cytotoxicity; concentrations ≥625 µg/mL caused cytotoxicity.	Microbiological Associates (1991)
Mutation	L5178Y TK ± mouse lymphoma cells	0, 50, 100, 200, 400, 800 µg/mL (Trial 1) 0, 80, 160, 320, 480, 640 µg/mL (Trial 2)	+	ND	Concentrations ≥640 µg/mL were cytotoxic; mutations were induced at concentrations of 400 µg/mL (Trial 1) and 480 µg/mL (Trial 2).	Mcgregor et al. (1991); NTP (1990)
Chromosomal aberrations (CAs)	Chinese hamster ovary (CHO) cells	0, 50, 160, 500 µg/mL without activation 0, 160, 500, 1,600 µg/mL with activation	−	−		NTP (1990); Galloway et al. (1987)

Table 4A. Summary of Benzaldehyde Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results[a]		Comments	References
			Without Activation	With Activation		
CAs	Chinese hamster lung cells	0, 0.8, 1.0 mg/mL without activation 0, 0.8, 1.0, 1.2 mg/mL with activation	+	−	Article was published in a Japanese language journal, but the abstract and tables are in English. Induction of CAs was observed at 1.0 mg/mL without S9.	Sofuni et al. (1985)
CAs	Chinese hamster B241 cell line	50 nM	+		The maximal frequency of aberration was observed at 50 nM without visible cytotoxicity; other test concentrations were not reported. It is unclear whether positive results were observed with or without metabolic activation (both conditions were evaluated).	Sofuni et al. (1985); Kasamaki et al. (1982)
Sister chromatid exchange (SCE)	CHO cells	0, 5, 16, 50, 160 µg/mL without activation 0, 160, 500, 1,600 µg/mL with activation	+	±	Induction of SCEs was observed at concentrations ≥50 µg/mL without S9 and ≥1,600 µg/mL with S9. The study authors considered benzaldehyde to be positive for the induction of SCEs in the absence of S9 and weakly positive in the presence of S9.	NTP (1990); Galloway et al. (1987)
SCE	Human lymphocytes	0–2.0 mM	+	ND	Benzaldehyde was observed to induce SCE in a dose-related manner.	Jansson et al. (1988)
DNA damage (comet assay)	Human lymphocytes	0, 1, 5, 10, 25, 50 mM	+	ND	Benzaldehyde increased DNA tail moment at 10 and 25 mM, and percent tail DNA increased at exposures ≥10 mM.	Demir et al. (2010)

Table 4A. Summary of Benzaldehyde Genotoxicity

Endpoint	Test System	Dose/ Concentration	Results[a]		Comments	References
			Without Activation	With Activation		
DNA protein cross-link (DPX)	Burkitt lymphoma cells (BLC); preparation of samples for DPX analysis was performed at both 4 and 65°C	0, 0.01, 0.1, 1, 5, 10, 25 mM	+	ND	Benzaldehyde caused significantly increased DPXs at concentrations ≥5 mM with 4°C washing and at 25 mM with 65°C washing. Cytotoxicity (≤60% cell viability) was noted at ≥10 mM.	Kuykendall et al. (2007)
Genotoxicity studies with extracellular purified DNA						
DNA cleavage	PM2 bacteriophage (supercoiled DNA)	Up to 15 mM	–	ND	Benzaldehyde did not induce DNA cleavage; however, benzaldehyde with $CuCl_2$ (up to 2 mM) caused a dose-dependent increase in DNA cleavage.	Becker et al. (1996)

[a]+ = positive, ± = equivocal or weakly positive, − = negative, NA = not applicable, ND = no data, NR = not reported.

Supporting Human Studies

Human health effects data are extremely limited. No adverse side effects were observed in a preliminary clinical trial that administered benzaldehyde in the form of β-cyclodextrin benzaldehyde (CBDA) orally or rectally at a dose of 2.5 mg CBDA/kg, 4 times/day for 2 weeks to 2 years (10 mg CBDA/kg-day) to terminal cancer patients (Kochi et al., 1980). CBDA is 8.3% benzaldehyde, so the approximate daily intake of benzaldehyde was 0.83 mg/kg-day; however, this study is difficult to interpret because no controls were used. No association between exposure to flavoring agents (including benzaldehyde) and impaired pulmonary function was observed in a cross-sectional study of flavoring manufacturing company workers; no exposure information was provided (Ronk et al., 2013). A case study reported the death of a young woman who drank 60 mL (approximately 900 mg/kg) of benzaldehyde, (based on a density of 1.050 g/mL and reference body weight of 70 kg); the time between consumption and death was not provided [Dadlez (1928) as cited in Anderson (2006)]. Findings at autopsy included a yellowish-white pulp in the stomach, a whitish, dry, and flushed mucous membrane, hyperemia in the small intestine, and ecchymotic spots on the pleura and pericardium.

Benzaldehyde may cause allergic skin reactions in certain individuals. In a case-report, a pastry chef with chronic urticaria tested positive to benzaldehyde in a patch test (Seite-Bellezza et al., 1994). Allergic contact dermatitis to benzaldehyde has also been reported in workers at a perfume factory (Schubert, 2006). Another study reported that only 1/50 patients with sensitivity to a fragrance mix containing benzaldehyde tested positive to benzaldehyde in a patch test [Becker et al. (1994) as cited in Anderson (2006)].

Supporting Animal Toxicity Studies

A number of supporting animal toxicity studies were identified (see Table 4B for additional details), including:

- An oral reproductive study in rats available only as summary in a secondary source that reported no significant effects following exposure to 5 mg/kg-day via gavage every other day for 32 weeks prior to mating, although it was noted that pregnancy rate was decreased in exposed dams [Sporn et al. (1967) as cited in Adams et al. (2005)].
- A teratogenicity screen in chick embryos that reported a low teratogenic potential for benzaldehyde (Abramovici and Rachmuth-Roizman, 1983).
- A subchronic-duration intraperitoneal (i.p.) study in rats that reported nasal and bronchial lesions after injection with 1 mg/day for 12 weeks (Schweinsberg et al., 1986).
- Acute oral lethality studies that reported median lethal dose (LD_{50}) values of 800−2,850 mg/kg in rats, 800−1,600 mg/kg in mice, and 1,000 mg/kg in guinea pigs [Jenner et al. (1964) and Sporn et al. (1967) as cited in Adams et al. (2005); Taylor et al., (1964) as cited in Anderson (2006); Schafer and Bowles (1985) as cited in IPCS (2001); Eastman Kodak (1991)].
- An acute inhalation study that reported reduced motor activity in mice following a 1-hour exposure to undiluted benzaldehyde vapors (Buchbauer et al., 1993).
- Two acute inhalation studies that reported RC_{50} (concentration that causes 50% response) values for reduced respiratory rate (indicating sensory irritation) of >6,177 mg/m^3 in rats and 1,450−1,710 mg/m^3 in mice (Babiuk et al., 1985; Steinhagen and Barrow, 1984).

- An acute inhalation lethality study that reported an LC_{50} value >5,504 mg/m^3 in rats (Eastman Kodak, 1991).
- Two acute skin irritation studies in guinea pigs; one reported no irritation (DuPont, 2000) and one reported moderate skin irritation (Eastman Kodak, 1991).
- Five skin sensitization studies in guinea pigs; four reported no sensitization (DuPont, 2000; Confidential, 1992, 1991b; Eastman Kodak, 1991) and one reported mild sensitization (Confidential, 1991a).
- An acute dermal lethality study that reported an LD_{50} value >20 mL/kg (Eastman Kodak, 1991).
- One ocular study that reported eye irritation with transient corneal damage (Eastman Kodak, 1991).

Metabolism/Toxicokinetic Studies

The absorption, distribution, metabolism, and elimination of benzaldehyde are well characterized and summarized below based on reviews by Adams et al. (2005), Anderson (2006), and IPCS (2006).

Benzaldehyde is rapidly absorbed following oral or inhalation exposure. Based on in vitro testing of human cadaver skin, dermal absorption occurs at a rate of 1,970 ± 720 µg/cm^2-hour in pure liquid form and 450 ± 70 µg/cm^2-hour in the saturated aqueous form. Following absorption, peak concentrations are reached in well-perfused tissues by 1.5 minutes and poorly perfused tissues by 12 minutes; after peak concentrations are achieved, benzaldehyde is rapidly cleared from tissues (half-life of ~10 minutes) in a linear fashion.

The principal metabolic path for benzaldehyde is rapid oxidization to benzoic acid via first-order kinetics; benzoic acid is then conjugated with glycine to form hippuric acid. A minor metabolic path is reduction into benzyl alcohol, which can react with glutathione as the sulfate conjugate to form benzylmercapturic acid. After biotransformation, benzaldehyde is almost exclusively eliminated via excretion in the urine in the form of hippuric acid (~70% of administered dose); other urinary metabolites include benzoyl glucuronic acid, benzyl glucuronide, free benzoic acid, and small amounts of benzylmercapturic acid. Urinary clearance is rapid, with metabolites detectable as early as 1.5 minutes following inhalation exposure.

Mode-of-Action/Mechanistic Studies/Therapeutic action

Mode-of-Action/Mechanistic Studies

Mechanistic studies regarding toxic effects of benzaldehyde exposure are limited [reviewed by Anderson (2006)]. Benzaldehyde has been shown to inhibit liver and lung metabolic enzymes, including CYP2B, CYP1A1, alcohol dehydrogenase, aryl hydrocarbon hydroxylase, and glutathione peroxidase. Benzaldehyde has also been shown to induce lipid peroxidation and generation of reactive oxygen species. Observed weight loss in rats following short-term and subchronic administration of high oral doses of benzaldehyde reported by NTP (1990) may be due to induction of lipolysis and glucose metabolism [reviewed by Anderson (2006)].

Table 4B. Other Supporting Studies

Test	Materials and Methods	Results	Conclusions	References
Reproductive (oral)	10 breeding age rats of an unspecified strain were administered approximately 0 or 5 mg/kg-d benzaldehyde via gavage every other day in oil (unspecified) for 32 wk. It is unclear if both males and females were exposed or just females. Rats were mated at D 75 and 180 and the following parameters were examined for each mating: number of pregnant females, number of offspring, pup body weights, and pup vitality.	No statistically significant differences were reported between the treatment and control groups. However, it was noted that fewer females in the benzaldehyde-treated group became pregnant compared with the control group (no data were provided).	Available data are inadequate to make a NOAEL/LOAEL determination.	Sporn et al., (1967) as cited in Adams et al. (2005)
Developmental (injection)	168 chicken embryos (white Leghorn × Rhode Island red strain) were injected suprablastodermically with 0, 0.025, 0.125, 0.25, 0.5, 1.25, 2.5, 3.75, 5.00, 12.5, or 25.00 µM/embryo benzaldehyde in olive oil on the third d of development. The numbers of dead embryos and embryos with malformations were determined daily until D 12 of development. Various other flavoring additives were evaluated in this study.	The optimal teratogenic dose (OTD), defined as "the concentration inducing a maximum teratogenic effect beyond the limits of the embryonic LD_{50}," was 25.00 µM/embryo. At the OTD, the percentage of abnormal embryos was 36.6% (compared with 7.9% in controls) and the percent mortality was 48.3% (compared with 17.8% in controls). The OTD for benzaldehyde was higher than the OTD for the majority of other flavoring additives.	The teratogenic potential of benzaldehyde is low compared with other flavoring agents.	Abramovici and Rachmuth-Roizman (1983)
Subchronic (i.p.)	Female SIV-50 rat (20/group) were administered 1 mg/d benzaldehyde via intraperitoneal (i.p.) injection for up to 12 wk; histopathological examination with a focus on the respiratory tract organs.	After 12 wk of benzaldehyde treatment, rats exhibited goblet cell hyperplasia, hyperplasia of the peribronchial lymphatic system, mucous epithelial atrophy, and accompanying perivasculitis.	Perivasculitis may have resulted from damage to the vessel walls or an allergic reaction.	Schweinsberg et al. (1986)
Acute lethality (oral)	Rats (10/group; unspecified strain and sex) were exposed once to benzaldehyde at doses of 200−3,200 mg/kg. Animals were observed for mortality and clinical signs of toxicity for 2 wk. Body weights were recorded prior to exposure and at the end of the 2-wk observation period.	All rats exposed to ≥1,600 mg/kg died; none of the rats exposed to <1,600 mg/kg died. Observed deaths occurred 1.5−4.5 hr after dosing. Clinical signs of toxicity included weakness, rough coat, diarrhea, and bloody urine.	Oral LD_{50} in rats = 800−1,600 mg/kg	Eastman Kodak (1991)
Acute lethality (oral)	White rats were exposed once to benzaldehyde at various (unspecified) doses. No further details were available.	No details were provided.	Oral LD_{50} in rats = 2,850 mg/kg	Sporn et al., (1967) as cited in Anderson (2006)

Table 4B. Other Supporting Studies

Test	Materials and Methods	Results	Conclusions	References
Acute lethality (oral)	Rats (10/sex/group) were exposed once to benzaldehyde via gavage at various (unspecified) doses. No further details were available.	All observed deaths occurred within 18 hr. Prior to death, rats showed depression or coma.	Oral LD_{50} (95% CI) in rats = 1,300 mg/kg (1,110−1,540 mg/kg)	Jenner et al., (1964) as cited in Anderson (2006)
Acute lethality (oral)	Osborne-Mendal and Sherman rats were exposed once to benzaldehyde at various (unspecified) doses. No further details were available.	All observed deaths occurred within 18 hr. Prior to death, rats showed depression or coma.	Oral LD_{50} in rats = 1,300 mg/kg	Taylor et al., (1964) as cited in Anderson (2006)
Acute lethality (oral)	Mice (10/group; unspecified strain) were exposed once to undiluted benzaldehyde at doses of 200−3,200 mg/kg. Animals were observed for mortality and clinical signs of toxicity for 2 wk. Body weights were recorded prior to exposure and at the end of the 2-wk observation period.	All mice exposed to ≥1,600 mg/kg died; none of the mice exposed to <1,600 mg/kg died. Observed deaths occurred 4−48 hr after dosing. Clinical signs of toxicity included weakness, ataxia, prostration, rough coat, sides "caved in".	Oral LD_{50} in mice = 800−1,600 mg/kg	Eastman Kodak (1991)
Acute lethality (oral)	Mice were exposed once to benzaldehyde at various (unspecified) doses via the diet. No further details were available.	No details were provided.	Oral LD_{50} in mice = 1,200 mg/kg	Schafer and Bowles (1985) as cited in IPCS (2001)
Acute lethality (oral)	Guinea pigs (number and strain unspecified) were exposed once to benzaldehyde via gavage at various (unspecified) doses. No further details were available.	All observed deaths occurred between 1 hr and 4 d after exposure. Prior to death, guinea pigs showed diuresis, tremors, intestinal irritation, and hemorrhage.	Oral LD_{50} (95% CI) in guinea pigs = 1,000 mg/kg (800−1,250 mg/kg)	Jenner et al., (1964) as cited in Anderson (2006)
Acute (inhalation)	Swiss outbred mice (sex and number unspecified) were exposed to undiluted benzaldehyde vapors for 1 hr. Motor activity was compared to unexposed controls.	Motor activity was decreased by 43.69% in benzaldehyde-exposed mice, compared with controls.	Benzaldehyde vapors have a mild sedative effect.	Buchbauer et al. (1993)
Acute (inhalation)	Male F344 rats (4/group) were exposed whole-body to increasing benzaldehyde concentrations in 10-min intervals (separated by 5-min recovery period) with or without a 9-d preexposure to 15 ppm formaldehyde (6 hr/d). The sensory irritation response was determined by measuring respiratory rate depression. The concentration needed to cause a 50% decrease in respiratory rate (RC_{50}) was calculated.	The RC_{50} was not identified; the RC_{30} was determined to be 1,423 ppm without formaldehyde preexposure. Preexposure to formaldehyde did not significantly alter the sensory irritation response.	Inhalation RC_{50} in rats >1,423 ppm (6,177 mg/m^3)	Babiuk et al. (1985)

Table 4B. Other Supporting Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	Male B6C3F$_1$ and Swiss-Webster mice (3/strain/group) were exposed head-only to increasing benzaldehyde concentrations in 10-min intervals (separated by 5-min recovery period). The sensory irritation response was determined by measuring respiratory rate depression. The concentration to cause a 50% decrease in respiratory rate (RD$_{50}$) was calculated.	RC$_{50}$ value (95% CI) in ppm: B6C3F$_1$ mice: 394 (312−522) Swiss-Webster mice: 333 (244−506)	Inhalation RC$_{50}$ in mice = 333−394 ppm (1,450–1,710 mg/m^3)	Steinhagen and Barrow (1984)
Acute lethality (inhalation)	3 rats (unspecified strain) were exposed to 1,268 ppm for 6 hr. Animals were observed for mortality and clinical signs of toxicity for 2 wk. Body weights were recorded prior to exposure and at the end of the 2-wk observation period.	No mortalities were observed. Transient clinical signs included eye blinking, nose-rubbing, accelerated respiration, and vasodilation.	Inhalation LC$_{50}$ >1,268 ppm (5,504 mg/m^3)	Eastman Kodak (1991)
Acute (dermal)	Benzaldehyde was tested for skin irritation and sensitization in 10 guinea pigs; it is unclear what concentration was used.	Benzaldehyde was nonirritating and nonsensitizing.	Benzaldehyde is not a skin irritant. Benzaldehyde is not a skin sensitizer.	DuPont (2000)
Acute (dermal)	Benzaldehyde was evaluated for skin sensitization in guinea pigs (10/group). Guinea pigs were given an initial intradermal injection of 0.1 mL of 3.0% benzaldehyde in paraffin oil followed by a challenge of topically applied 7−15% benzaldehyde in petrolatum (occluded for 24 hr). Skin was evaluated at 24 and 48 hr.	No positive reactions were observed.	Benzaldehyde is not a skin sensitizer.	Confidential (1992)
Acute (dermal)	Benzaldehyde was evaluated for skin sensitization in guinea pigs (10/group). Guinea pigs were given an initial intradermal injection of 0.1 mL of 2.7% benzaldehyde in paraffin oil followed by 3 challenges of topically applied 0.24–2.4% benzaldehyde in petrolatum (occluded for 24 hr). Skin was evaluated at 24 and 48 hr.	No positive reactions were observed.	Benzaldehyde is not a skin sensitizer.	Confidential (1991b)

Table 4B. Other Supporting Studies

Test	Materials and Methods	Results	Conclusions	References
Acute (dermal)	Benzaldehyde was evaluated for skin sensitization in guinea pigs (10/group). Guinea pigs were given an initial intradermal injection of 0.1 mL of 2.7% benzaldehyde in paraffin oil followed by 2 challenges of topically applied 2.1% benzaldehyde in petrolatum, and a third challenge of 0.64% benzaldehyde in petrolatum (occluded for 24 hr). Skin was evaluated at 24 and 48 hr.	In Challenge 1 and 2, 2/10 animals had a positive response. In Challenge 3, 0/10 animals had a positive response.	Based on response rate of 20%, benzaldehyde is classified as a weak sensitizer.	Confidential (1991a)
Acute (dermal)	Gauze pads soaked in 5–20 mL/kg undiluted benzaldehyde were applied to depilated skin of guinea pigs (3/group) for 24 hr. Guinea pigs were observed for mortality, skin changes, and clinical signs of toxicity for 2 wk. Body weights were recorded prior to exposure and at the end of the 2-wk observation period.	Benzaldehyde was a moderate skin irritant. The study authors noted that animals receiving the highest dose gained less weight than animals receiving the lowest dose (data not provided). No mortalities were observed.	Benzaldehyde is a moderate skin irritant. Dermal LD_{50} >20 mL/kg	Eastman Kodak (1991)
Acute (dermal)	Benzaldehyde was evaluated for skin sensitization in guinea pigs (5/group). Skin was evaluated for 48 hr. No further information was reported.	Benzaldehyde was nonsensitizing.	Benzaldehyde is not a skin sensitizer.	Eastman Kodak (1991)
Acute (ocular)	1 drop of undiluted benzaldehyde was dropped in the eye of a rabbit. The eye was monitored for 48 hr.	Immediate irritant effects were noted, with corneal damage within 24 hr. Only erythema persisted at 48 hr.	Benzaldehyde is an eye irritant, causing transient corneal damage.	Eastman Kodak (1991)

CI = confidence interval.

Therapeutic Action

Benzaldehyde has been proposed as an antitumor/carcinostatic agent. An early clinical trial suggested that oral or rectal administration of benzaldehyde in the form of CBDA may halt or reverse tumor progression (Kochi et al., 1980) (see experimental details above in "Supporting Human Studies"). However, results are difficult to interpret due to inconsistent treatment durations, various tumor types, and lack of control subjects. No additional antitumor studies in humans have been identified. In animal models, benzaldehyde has led to the reduction of tumor weights in mice implanted with adenocarcinomas; however, it was either ineffective or only marginally effective against the advancement of terminal solid tumors in dogs and cats [reviewed by Anderson (2006)]. Numerous in vitro studies indicate that benzaldehyde is cytotoxic, antiproliferative, and/or induces apoptosis in primary or transformed mammalian cell lines [reviewed by Anderson (2006)].

Benzaldehyde has also been proposed as an antiallergy agent. Oral benzaldehyde treatment reduced allergic responses in murine models of allergic asthma and rhinitis; the proposed mechanism was via inhibition of hypoxia-inducible factor 1 (HIF-1α) and vascular endothelial growth factor (VEGF) (Jang et al., 2014). Additionally, oral benzaldehyde treatment reduced ovalbumin (OA)-induced bronchoconstriction, decreased eosinophils, neutrophils, and bronchoconstrictor mediators, $LTC_4/D_4/E_4$, in bronchoalveolar lavage fluid, and increased bronchodilator mediator, prostaglandin E_2 (PGE_2), in bronchoalveolar lavage fluid in OA-sensitized guinea pigs (Lacroix et al., 2002).

DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer reference values, respectively.

Table 5. Summary of Noncancer Reference Values for Benzaldehyde (CASRN 100-52-7)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/male and female	Mortality and reduced body weight in males; necrotic/degenerative lesions of the brain, liver, and kidney, and hyperplasia and hyperkeratosis of the forestomach in both sexes	2×10^{-1}	$NOAEL_{HED}$	68.6	300	NTP (1990)
Chronic p-RfD	Oral RfD value is available on IRIS.						
Subchronic p-RfC	NDr						
Chronic p-RfC	NDr						

NDr = not determined.

Table 6. Summary of Cancer Reference Values for Benzaldehyde (CASRN 100-52-7)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value	Principal Study
Provisional oral slope factor (p-OSF) $(mg/kg\text{-}d)^{-1}$	Mouse/female	Forestomach squamous cell papilloma	4×10^{-3}	NTP (1990)
Provisional inhalation unit risk (p-IUR) $(mg/m^3)^{-1}$	NDr			

NDr = not determined.

DERIVATION OF ORAL REFERENCE DOSES

The database of potentially relevant studies for derivation of oral reference values for benzaldehyde includes 16-day, 13-week, and 2-year studies in rats and mice sponsored by the NTP (NTP, 1990; Kluwe et al., 1983) and 16- and 28-week studies in rats (Hagan et al., 1967). A subchronic provisional oral reference dose (p-RfD) is derived based on the available studies. A chronic p-RfD is not derived because there is an oral RfD value on EPA's IRIS database.

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The NTP (1990) subchronic-duration study in rats was selected as the principal study for derivation of the subchronic p-RfD. Critical effects from this study were mortality in males; reduced body weight in surviving males; necrotic and degenerative lesions of the brain, liver, and kidney in males and females; and proliferative lesions in the forestomach in males and females.

Justification of the Principal Study

A comparison of the results from the 13-week gavage studies in rats and mice (NTP, 1990) indicated that the rat was more sensitive than the mouse. In the rat, mortality of males occurred at a lower dose than in mice, lesions were found in the brain, liver, and forestomach, in addition to the kidney (in mice, only kidney lesions were observed), and lesions were found in both sexes (no effects were seen in female mice). Therefore, the subchronic-duration NTP (1990) rat study was selected as the principal study for derivation of the subchronic p-RfD. This study is a peer-reviewed published study with an adequate number of dose groups and dose spacing, sufficient group sizes, and quantitation of results to describe dose-response relationships for the critical effects in rats associated with subchronic oral exposure to benzaldehyde.

Short-term-duration gavage studies in rats and mice were not selected as principal studies because of the brief exposure duration (NTP, 1990). Chronic-duration studies in rats and mice (NTP, 1990) demonstrated effects at lower doses than the subchronic-duration studies, but were not selected as principal studies for the subchronic p-RfD derivation due to the near-lifetime exposure duration.

Justification of the Critical Effect

Mortality was increased at the lowest doses causing adverse effects across short-term, subchronic, and chronic exposure durations, although limited to males of both species in the subchronic-duration studies and male rats in the chronic-duration studies (see Table 3A). Mortality was the most sensitive effect identified in the short-term-duration NTP (1990) studies in both rats and mice. Reduced body weight was also seen in survivors among the rats. Mortality was also among the most sensitive effects found in the subchronic-duration NTP

(1990) rat and mouse studies, although in these studies, it occurred only in males, and organ effects were observed as well (necrotic/degenerative lesions of the brain, liver, and kidney, and hyperplasia and hyperkeratosis of the forestomach in male and female rats; degenerative kidney lesions in male mice). In the chronic-duration studies (NTP, 1990) mortality was again among the critical effects in male rats; in this case, hyperplasia of the pancreas was seen in surviving animals. Proliferative lesions in the forestomach were the most sensitive findings in chronically exposed mice, at the same dose that caused mortality in male rats. Mortality, reduced body weight, and lesions occurring at the same dose were selected as cocritical effects for derivation of the subchronic p-RfD.

Approach for Deriving the Subchronic p-RfD

The $NOAEL_{ADD}$ of 286 mg/kg-day is the selected point of departure (POD) for derivation of the subchronic p-RfD. Data for all cocritical endpoints were not amenable to benchmark dose (BMD) modeling because all effects were seen only in the high-dose group.

In *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Other approaches may include using some chemical-specific information, without a complete physiologically based toxicokinetic model. In lieu of chemical-specific models or data to inform the derivation of human equivalent oral exposures, EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions. More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not for portal-of-entry effects.

A validated human physiologically based pharmacokinetic (PBPK) model for benzaldehyde is not available for use in extrapolating doses from animals to humans. In addition, the selected POD of 286 mg/kg-day is based on systemic effects, which are not portal-of-entry effects. Therefore, scaling by $BW^{3/4}$ is relevant for deriving human equivalent doses (HEDs) for this effect.

Following U.S. EPA (2011b) guidance, the POD for the subchronic study in rats (NTP, 1990) is converted to a HED through the application of a DAF derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where:

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a reference BW_a of 0.25 kg for rats and a reference BW_h of 70 kg for humans (U.S. EPA, 1988b), the resulting DAF is 0.24. Applying this DAF to the $NOAEL_{ADD}$ of 286 mg/kg-day yields a $NOAEL_{HED}$ of 70 mg/kg-day, as follows:

$$NOAEL_{HED} = NOAEL_{ADD} \text{ (mg/kg-day)} \times DAF$$
$$= 286 \text{ mg/kg-day} \times 0.24$$
$$= 70 \text{ mg/kg-day}$$

The subchronic p-RfD for benzaldehyde, based on a $NOAEL_{HED}$ of 70 mg/kg-day for mortality, decreased body weight, and degenerative tissue lesions, is derived as follows:

$$\textbf{Subchronic p-RfD} = NOAEL_{HED} \div UF_C$$
$$= 70 \text{ mg/kg-day} \div 300$$
$$= \mathbf{2 \times 10^{-1} \text{ mg/kg-day}}$$

Table 7 summarizes the UFs for the subchronic p-RfD for benzaldehyde.

Table 7. Uncertainty Factors for Subchronic p-RfD for Benzaldehyde

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF_H	10	A UF_H of 10 is applied to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of benzaldehyde in humans.
UF_D	10	A UF_D of 10 has been applied because there are no acceptable two-generation reproductive or developmental toxicity studies for benzaldehyde via the oral route.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because the critical study has a subchronic duration.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

The confidence in the subchronic p-RfD for benzaldehyde is medium as explained in Table 8 below.

Table 8. Confidence Descriptors for the Subchronic p-RfD for Benzaldehyde

Confidence Categories	Designation[a]	Discussion
Confidence in principal study	M	The confidence in the principal study is medium. The study was of appropriate duration and included histopathology, but organ weight, hematology, and clinical chemistry analyses were not conducted. The study identified a NOAEL, but frank effects were seen at the lowest effect level (LOAEL).
Confidence in database	M	The confidence in the database is medium. The database includes NTP-sponsored short-term-, subchronic-, and chronic-duration studies in male and female rats and mice. However, clinical chemistry and hematology were not performed in these studies. Hematology was assessed in the 16-wk study by Hagan et al. (1967); however, data reporting in this study are inadequate for independent review. Additionally, no two-generation reproduction studies or developmental studies are available. A single-generation reproduction study indicated possible effects on reproduction, even though no statistically significant changes were found; however, this report was only available as a summary in a secondary source, and numerical data were not available for independent review [Sporn et al. (1967) as cited in Adams et al. (2005)].
Confidence in subchronic p-RfD	M	The overall confidence in the subchronic p-RfD is medium.

[a]M = medium.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

A chronic p-RfD value is not derived because an oral RfD value is available on EPA's IRIS database.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

Human and animal data are inadequate to derive subchronic or chronic provisional inhalation reference concentrations (p-RfCs) for benzaldehyde. There is a single short-term-duration inhalation study available for benzaldehyde inhalation in rats (Laham et al., 1991). This study is of insufficient duration to serve as basis for an inhalation reference value.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

The cancer weight of evidence (WOE) for oral exposure to benzaldehyde is *"Suggestive Evidence of Carcinogenic Potential;"* the cancer WOE for inhalation exposure to benzaldehyde is *"Inadequate Information to Assess Carcinogenic Potential"* (see the details below and in Table 9).

Following U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, the database for oral exposure to benzaldehyde provides *suggestive evidence of carcinogenic potential.* This descriptor is based on a significant increase in forestomach papilloma in female mice, a near-significant trend for increased forestomach papilloma in male mice, and significant increases in preneoplastic forestomach lesions (hyperplasia) in male and female mice exposed to benzaldehyde via gavage for 104 weeks, which NTP (1990) considered to provide "some

evidence of carcinogenicity." There was no evidence of carcinogenicity in rats in a companion 2-year bioassay (NTP, 1990), and no other relevant human or animal data were located.

Following U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment,* the database for inhalation exposure to benzaldehyde provides *inadequate information to assess carcinogenic potential.* No human or chronic-duration animal inhalation studies have been identified.

Table 9. Cancer Weight-of-Evidence Descriptor for Benzaldehyde

Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
"Carcinogenic to Humans"	NS	NA	There are no human data to support this.
"Likely to Be Carcinogenic to Humans"	NS	NA	Results from available animal studies are not sufficient to support this, and no human data are available.
"Suggestive Evidence of Carcinogenic Potential"	**Selected**	**Oral**	**NTP (1990) conducted carcinogenicity studies in rats and mice. In mice, NTP concluded there was "some evidence of carcinogenicity" based on significant increases in forestomach papilloma in females, a "near-significant" trend for increased forestomach papilloma in males, and significant increases in preneoplastic forestomach lesions (hyperplasia) in both sexes. In rats, there was no evidence of carcinogenicity.**
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Inhalation**	**There are no human or animal inhalation carcinogenicity studies available.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	The available data do not support this.

NA = not applicable, NS = not selected.

MODE-OF-ACTION (MOA) DISCUSSION

The *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 2005) define MOA "…as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation." Examples of possible modes of carcinogenic action for any given chemical include "mutagenicity, mitogenesis, programmed cell death, cytotoxicity with reparative cell proliferation, and immune suppression" (pp. 1−10).

A carcinogenic MOA of benzaldehyde is not known. The available evidence suggests that benzaldehyde is equivocally mutagenic, but may cause DNA damage and clastogenic effects (see "Genotoxicity Studies" section for more details). Forestomach tumors in female mice following chronic oral exposure to benzaldehyde (NTP, 1990) might be hypothesized to result from cytotoxicity followed by sustained regenerative cell proliferation. In support, forestomach

hyperplasia was increased in a dose-related manner in both male and female mice following chronic exposure to benzaldehyde (NTP, 1990), and the cytotoxicity of benzaldehyde has been demonstrated in numerous in vitro studies [reviewed by Anderson (2006)]. However, benzaldehyde has also been shown to have antiproliferative and apoptotic effects on transformed cell lines, and is a proposed anticancer agent [reviewed by Anderson (2006)]. No firm conclusion regarding possible MOAs for benzaldehyde carcinogenicity can be made, and a mutagenic mode of action cannot be ruled out. Thus, a linear approach is applied as recommended by U.S. EPA (2005).

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

An NTP 2-year bioassay in rats and mice was available for the development of a provisional oral slope factor (p-OSF) (NTP, 1990). This study was conducted in accordance with good laboratory practice (GLP) principles, was peer reviewed, and meets the standards of study design and performance with respect to the number of animals used, the examination of potential toxicity endpoints, and the presentation of information.

No clear evidence of carcinogenicity was observed in the rat study. However, in the mouse study, NTP (1990) concluded that there was "some evidence of carcinogenicity" in male and female mice based on increases in the incidences of squamous cell papilloma and hyperplasia of the forestomach. The increased incidence of squamous cell papilloma was only statistically significant in female mice, but "near significant ($p = 0.057$)" in males. Forestomach tumor incidence in female mice was selected for BMD modeling. Prior to modeling, all doses were converted to HEDs using $BW^{3/4}$ scaling, as recommended by the U.S. EPA (2011b); see the Derivation of a Subchronic p-RfD section for more details. Following U.S. EPA (2011b) guidance, the administered doses for the chronic-duration study in mice are converted to HED doses through the application of a DAF derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

where:

DAF = dosimetric adjustment factor
BW_a = animal body weight
BW_h = human body weight

Using a reference BW_a of 0.025 kg for mice and a reference BW_h of 70 kg for humans (U.S. EPA, 1988b), the resulting DAF is 0.14. HED doses of 30.0 or 60.1 mg/kg-day in females were calculated as follows:

$$\begin{aligned} \text{Low-dose}_{HED} &= \text{low-dose (mg/kg-day)} \times (\text{days per week}/7) \times DAF \\ &= 214 \text{ mg/kg-day} \times (5/7) \times 0.14 \\ &= 30.0 \text{ mg/kg-day} \end{aligned}$$

$$\begin{aligned} \text{High-dose}_{HED} &= \text{high-dose (mg/kg-day)} \times (\text{days per week}/7) \times DAF \\ &= 429 \text{ mg/kg-day} \times (5/7) \times 0.14 \\ &= 60.1 \text{ mg/kg-day} \end{aligned}$$

Based on BMD modeling, a 10% benchmark dose lower confidence limit human equivalent dose ($BMDL_{10HED}$) of 25.7 mg/kg-day was calculated (see Table 10; additional BMD details in Appendix C). The $BMDL_{10HED}$ of 25.7 mg/kg-day was used as the POD for derivation of the p-OSF.

Table 10. BMD Model Results for Derivation of the p-OSF[a]

Reference	Tumor Endpoint	Model Type	Goodness-of-Fit *p*-Value	AIC	BMD_{10HED} (mg/kg-d)	$BMDL_{10HED}$ (mg/kg-d)	p-OSF $(mg/kg\text{-}d)^{-1}$
NTP (1990)	Forestomach squamous cell papilloma in female mice	Multistage-cancer-1st order	0.7076	71.86	40.6	25.7	4×10^{-3}

[a]All modeling was conducted using U.S. EPA BMDS (Version 2.5). BMD analysis details are available in Appendix C.

The p-OSF is derived as follows:

$$\begin{aligned} \textbf{p-OSF} &= \text{Benchmark response (BMR)} \div BMDL_{10HED} \\ &= 0.10 \div 25.7 \text{ mg/kg-day} \\ &= \mathbf{4.0 \times 10^{-3}\ (mg/kg\text{-}day)^{-1}} \end{aligned}$$

Derivation of Provisional Inhalation Unit Risk (p-IUR)

The lack of data on the carcinogenicity of benzaldehyde following inhalation exposure precludes the derivation of a quantitative estimate (p-IUR) for inhalation exposure.

APPENDIX A. SCREENING PROVISIONAL VALUES

No provisional screening values are derived.

APPENDIX B. DATA TABLES

Table B-1. Survival and Terminal Body Weights of Male and Female F334/N Rats Administered Benzaldehyde via Gavage 5 Days/Week for 16 Days[a]

Parameter	Dose Group, mg/kg-d (ADD, mg/kg-d)[b]					
	0 (0)	**100 (71.4)**	**200 (143)**	**400 (286)**	**800 (571)**	**1,600 (1,143)**
Males						
Survival	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	3/5 (60%)	0/5[c] (0%)
Terminal body weight (g)[d]	238 ± 6	228 ± 6 (−4%)	229 ± 4 (−4%)	240 ± 4 (+1%)	204 ± 8[c] (−14%)	NA[e]
Females						
Survival	5/5 (100%)	5/5 (100%)	5/5 (100%)	5/5 (100%)	3/5 (60%)	0/5[c] (0%)
Terminal body weight (g)[d]	151 ± 2	140 ± 2[c] (−7%)	145 ± 3 (−4%)	154 ± 4 (+2%)	135 ± 2[c] (−11%)	NA[e]

[a]NTP (1990).
[b]ADD (adjusted daily dose) = dose × (5 days/7 days).
[c]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test, student's *t*-test; 2-tailed).
[d]Values are expressed as mean ± standard error of the mean (SEM) (percent change compared with control) for rats surviving to 16 days; % change control = [(treatment mean – control mean)/control mean] × 100
[e]NA = not applicable; no body weight data were presented by the study authors due to 100% mortality in the highest dose animals.

Table B-2. Survival and Terminal Body Weights of Male and Female F334/N Rats Administered Benzaldehyde via Gavage 5 Days/Week for 13 Weeks[a]

Parameter	Dose Group, mg/kg-d (ADD, mg/kg-d)[b]					
	0 (0)	**50 (36)**	**100 (71.4)**	**200 (143)**	**400 (286)**	**800 (571)**
Males						
Survival	10/10 (100%)	10/10 (100%)	10/10 (100%)	10/10 (100%)	10/10 (100%)	4/10[c] (40%)
Terminal body weight (g)[d]	340 ± 5	338 ± 6 (−1%)	346 ± 6 (+2%)	349 ± 6 (+3%)	329 ± 8 (−3%)	252 ± 5[c] (−26%)
Females						
Survival	9/10 (90%)	10/10 (100%)	10/10 (100%)	10/10 (100%)	9/10 (90%)	7/10 (70%)
Terminal body weight (g)[d]	203 ± 3	196 ± 4 (−3%)	203 ± 3 (+0%)	200 ± 4 (−1%)	203 ± 3 (+0%)	213 ± 4 (+5%)

[a]NTP (1990).
[b]ADD (adjusted daily dose) = dose × (5 days/7 days).
[c]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test, student's *t*-test; 2-tailed).
[d]Values are expressed as mean ± SEM (percent change compared with control) for rats surviving to 16 days; % change control = [(treatment mean – control mean)/control mean] × 100.

Table B-3. Histopathological Findings in Male and Female F344 Rats Administered Benzaldehyde via Gavage 5 Days/Week for 13 Weeks[a]

Parameter[b]		Dose Group, mg/kg (ADD, mg/kg-d)[c]		
		0	400 (286)	800 (571)
Males				
Brain	Cerebellum degeneration	0/10 (0%)	0/10 (0%)	9/10** (90%)
	Cerebellum necrosis	0/10 (0%)	0/10 (0%)	10/10** (100%)
	Cerebellum mineralization	0/10 (0%)	0/10 (0%)	7/10** (70%)
	Hippocampus necrosis	0/10 (0%)	0/10 (0%)	6/6** (100%)
Forestomach[d]	Hyperplasia	0/10 (0%)	0/10 (0%)	6/10** (60%)
	Hyperkeratosis	0/10 (0%)	0/10 (0%)	5/10* (50%)
Liver	Degeneration	0/10 (0%)	0/10 (0%)	4/10* (40%)
	Necrosis	0/10 (0%)	0/10 (0%)	3/10 (30%)
Kidney	Tubule degeneration	0/10 (0%)	0/10 (0%)	4/10* (40%)
	Tubule necrosis	0/10 (0%)	0/10 (0%)	3/10 (30%)
Females				
Brain	Cerebellum degeneration	0/9 (0%)	0/10 (0%)	10/10** (100%)
	Cerebellum necrosis	0/9 (0%)	0/10 (0%)	10/10** (100%)
	Cerebellum mineralization	0/9 (0%)	0/10 (0%)	0/10 (0%)
	Hippocampus necrosis	0/9 (0%)	0/10 (0%)	10/10** (100%)
Forestomach[d]	Hyperplasia	0/9 (0%)	0/10 (0%)	8/10** (80%)
	Hyperkeratosis	0/9 (0%)	0/10 (0%)	6/10** (60%)
Liver	Degeneration	0/9 (0%)	0/10 (0%)	4/10* (40%)
	Necrosis	0/9 (0%)	0/10 (0%)	0/10 (0%)
Kidney	Tubule degeneration	0/9 (0%)	0/10 (0%)	4/10* (40%)
	Tubule necrosis	0/9 (0%)	0/10 (0%)	3/10 (30%)

[a]NTP (1990). Note: not all dose groups were examined histologically.
[b]Results are expressed as the number of animals with lesions/number of animals examined (%).
[c]ADD (adjusted daily dose) = dose × (5 days/7 days).
[d]Kluwe et al. (1983) reported that 2/10 males had forestomach hyperplasia and hyperkeratosis at 400 mg/kg-day; this finding was used to identify a NOEL and LOAEL of 200 and 400 mg/kg-day for the 1988 IRIS assessment (U.S. EPA, 2003).
*Statistically significantly different from control ($p < 0.05$); as determined by the study authors.
**Statistically significantly different from control ($p < 0.01$); as determined by the study authors.

Table B-4. Survival and Select Neoplastic and Preneoplastic Lesions in Male F344 Rats Administered Benzaldehyde via Gavage 5 Days/Week for 103 Weeks[a]

Parameter[b]	Dose Group, mg/kg (ADD, mg/kg-d)[c]		
	0	**200 (143)**	**400 (286)**
Survival	37/50† (74%)	29/50 (58%)	21/50* (42%)
Pancreas			
Hyperplasia	6/49 (12%)	6/49 (12%)	12/48†* (25%)
Adenoma[d]	3/49 (6%)	2/49 (4%)	7/48†* (15%)
Mesothelium			
Mesothelioma[e]	0/50 (0%)	5/50* (10%)	2/50 (4%)
Hematopoeitic system			
Mononuclear cell leukemia			
All stages[f]	10/50† (20%)	17/50* (34%)	16/50* (32%)
Stage 1	4/50 (8%)	10/50 (20%)	7/50 (14%)
Stage 2 and 3 (combined)	6/50 (12%)	7/50 (14%)	9/50 (18%)

[a]NTP (1990).
[b]Results expressed as the number of animals observed with lesion/number of animals examined for that lesion (% incidence). Statistical results in the control column represent the trend test, while the statistical results in the dosed columns represent pairwise comparisons with the vehicle control.
[c]ADD (adjusted daily dose) = dose × (5 days/7 days).
[d]The historical control incidence range of pancreatic acinar cell neoplasms (adenomas or carcinomas combined) at the study laboratory is 0/49−11/50 (0–22%). The mean historical control incidence at the study laboratory (mean ± SD) is 36/397 (9 ± 9%). The mean historical control incidence in NTP studies (mean ± SD) is 107/2,011 (5 ± 7%).
[e]The mean historical control incidence for mesotheliomas at the study laboratory (mean ± SD) is 15/450 (3 ± 3%). The mean historical control incidence in NTP studies (mean ± SD) is 78/2,099 (4 ± 3%).
[f]The mean historical control incidence of leukemia at the study laboratory (mean ± SD) is 45/450 (10 ± 8%). The mean historical control incidence in NTP studies (mean ± SD) is 361/2,099 (17 ± 9%).
*Statistically significantly different from controls at $p < 0.05$, as reported by the study authors.
†Statistically significant dose-related trend ($p < 0.05$), as reported by the study authors.

Table B-5. Survival and Neoplastic and Preneoplastic Forestomach Lesions in Male and Female B6C3F1 Mice Exposed to Benzaldehyde via Gavage 5 Days/Week for 103−104 Weeks[a]

Parameter[b]	Exposure Group mg/kg-d (ADD, mg/kg-d)[c]		
Males	**0**	**200 (143)**	**400 (286)**
Survival	32/50 (64%)	33/50 (66%)	31/50 (62%)
Focal hyperplasia	7/50 (14%)	8/50 (16%)	16/50** (32%)
Squamous cell papilloma[d]	1/50 (2%)	2/50 (4%)	5/50[N.S] (10%)
Females	**0**	**300 (214)**	**600 (429)**
Survival	30/50 (60%)	27/50 (54%)	35/50 (70%)
Focal hyperplasia	12/50 (24%)	23/50* (46%)	39/50** (78%)
Squamous cell papilloma[d]	0/50† (0%)	5/50* (10%)	6/50* (12%)

[a]NTP (1990).
[b]Results expressed as the number of animals observed with lesion/number of animals examined for that lesion (% incidence). Statistical results in the control column represent the trend test, while the statistical results in the dosed columns represent pairwise comparisons with the vehicle control.
[c]ADD (adjusted daily dose) = dose × (5 days/7 days).
[d]The mean historical control incidence of squamous cell papillomas and/or carcinomas (combined) of the forestomach at the study laboratory (mean ± SD) is 8/445 (2 ± 4%) for males and 8/446 (2 ± 3%) for females. The mean historical control incidence reported in NTP studies (mean ± SD) is 39/2,033 (2 ± 3%) for males and 33/2,047 (2 ± 3%) for females.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.
†Statistically significant dose-related trend ($p < 0.05$), as reported by the study authors.
[N.S.]"Near-significant" dose-related trend ($p = 0.057$), as reported by the study authors.

Table B-6. Survival and Terminal Body and Liver Weights of Male and Female Sprague-Dawley Rats Exposed to Benzaldehyde via Inhalation 6 Hours/Day for 14 Days[a]

Parameter	Exposure, mg/m^3 (HEC_{ER})[b]			
	0	2,170 (543)	3,260 (815)	4,341 (1,085)
Male				
Survival	14/14 (100%)	14/14 (100%)	14/14 (100%)	13/14 (93%)
Terminal body weight[c] (g)	348 ± 5	327 ± 4** (−6%)	322 ± 4*** (−7%)	322 ± 6** (−7%)
Liver				
Relative[c] (g)	NR[d]	NR	NR	NR
Liver-to-body weight ratio	2.50 ± 0.08	2.96 ± 0.02* (+18%)	NR	NR
Female				
Survival	14/14 (100%)	14/14 (100%)	11/14 (79%)	4/14 (29%)
Terminal body weight[c] (g)	224 ± 2	227 ± 2 (+1%)	222 ± 1 (−1%)	221 ± 5 (−1%)
Liver				
Absolute[c] (g)	6.10 ± 0.08	8.00 ± 0.02* (+31%)	7.60 ± 0.02* (+25%)	7.00 ± 0.02* (+15%)
Liver-to-body weight ratio	2.70 ± 0.10	3.52 ± 0.06 (+30%)*	3.40 ± 0.02* (+26%)	3.10 ± 0.20* (+15%)

[a]Laham et al. (1991).
[b]HEC_{ER} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × ratio of blood:gas partition coefficient (animal:human) [default value of 1].
[c]Weights expressed as mean ± SEM (percent change compared with control) for rats surviving until sacrifice on Day 14; % change control = [(treatment mean – control mean)/control mean] × 100.
[d]NR = values were not reported by the study authors, however, the authors stated there were no significant increases in these treated group.
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p < 0.01$), as reported by the study authors.
***Statistically significantly different from control ($p < 0.001$), as reported by the study authors.

Table B-7. Selected Hematology Parameters of Male and Female Sprague-Dawley Rats Exposed to Benzaldehyde via Inhalation 6 Hours/Day for 14 Days[a]

Parameter[b]	Exposure, mg/m^3 (HEC_{ER})[c]			
	0	2,170 (543)	3,260 (815)	4341 (1,085)
Male				
RBCs (× 10^{12}/L)	6.3 ± 0.1	6.3 ± 0.1 (+0%)	7.1 ± 0.2* (+13%)	6.2 ± 0.05 (−2%)
Hematocrit (L/L)	0.37 ± 0.004	0.37 ± 0.009 (+0%)	0.41 ± 0.007* (+11%)	0.35 ± 0.004* (−5%)
Hemoglobin (g/L)	140.0 ± 2.0	137.0 ± 3.0 (−2%)	144.0 ± 2.0 (+3%)	125.0 ± 2.0* (−11%)
MCH (pg)	22.2 ± 0.3	21.7 ± 0.2 (−2%)	20.3 ± 0.2* (−9%)	20.2 ± 0.3* (−9%)
MCHC (g/L)	378.4 ± 2.0	370.3 ± 2.0 (−2%)	351.2 ± 1.0* (−7%)	357.0 ± 3.0* (−6%)
WBCs (× 10^9/L)	9.4 ± 0.5	11.5 ± 1.2 (+22%)	11.0 ± 1.0 (+17%)	12.7 ± 0.2* (+35%)
Monocytes (× 10^9/L)	0.12 ± 0.06	0.20 ± 0.1 (+67%)	0.31 ± 0.08 (+158%)	0.06 ± 0.03 (−50%)
Female				
RBCs (× 10^{12}/L)	6.3 ± 0.1	6.4 ± 0.1 (+2%)	6.4 ± 0.1 (+2%)	5.8 ± 0.1* (−8%)
Hematocrit (L/L)	0.34 ± 0.004	0.35 ± 0.006 (+3%)	0.36 ± 0.005 (+6%)	0.33 ± 0.003* (−3%)
Hemoglobin (g/L)	133.0 ± 2.0	133.0 ± 1.0 (+0%)	133.0 ± 2.0 (+0%)	125.0 ± 2.0* (−6%)
MCH (pg)	21.1 ± 0.3	20.8 ± 0.4 (−1%)	20.8 ± 0.2 (−1%)	21.6 ± 0.5 (+2%)
MCHC (g/L)	391.2 ± 5.0	380.0 ± 6.0 (−3%)	369.4 ± 3.0* (−6%)	378.8 ± 6.0 (−3%)
WBCs (× 10^9/L)	7.5 ± 0.8	9.7 ± 0.7 (+29%)	9.0 ± 1.7 (+20%)	8.2 ± 1.0 (−6%)
Monocytes (× 10^9/L)	0.02 ± 0.008	0.19 ± 0.05* (+850%)	0.21 ± 0.03* (+950%)	0.15 ± 0.02* (+650)

[a]Laham et al. (1991).
[b]Results expressed as mean ± SEM (percent change compared with control) for 4–6 rats/group; % change control = [(treatment mean – control mean)/control mean] × 100.
[c]HEC_{ER} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × ratio of blood-gas partition coefficient (animal:human) [default value of 1].
*Statistically significantly different from control ($p < 0.05$); as reported by the study authors.

Table B-8. Selected Clinical Chemistry Parameters of Male and Female Sprague-Dawley Rats Exposed to Benzaldehyde via Inhalation 6 Hours/Day for 14 Days[a]

Parameter[b]	Exposure, mg/m^3 (HEC_{ER})[c]			
	0	2,170 (543)	3,260 (815)	4,341 (1,085)
Male				
Albumin (g/L)	32.0 ± 0.2	32.0 ± 0.5 (0%)	33.0 ± 0.4** (+3%)	35.0 ± 4.0 (+9%)
Total protein (g/L)	55.0 ± 0.8	54.0 ± 1.0 (−2%)	56.0 ± 0.8 (+2%)	55.0 ± 1.0 (+0%)
Cholinesterase (U/L)	648.7 ± 21.2	643.2 ± 15.4 (−1%)	639.0 ± 11.8 (+1%)	735.0 ± 33.0 (+13%)
AST (U/L)	88.5 ± 5.7	123.0 ± 6.5 ** (+39%)	139.6 ± 8.5*** (+58%)	116.2 ± 5.7 ** (+31%)
ALT (U/L)	39.3 ± 6.0	48.3 ± 1.4 (+23%)	53.6 ± 2.9 (+36%)	44.3 ± 1.9 (+13%)
Female				
Albumin (g/L)	36.0 ± 0.5	33.0 ± 0.4** (−8%)	32.0 ± 0.5*** (−11%)	32.0 ± 0.2*** (−11%)
Total protein (g/L)	61.0 ± 1.0	58.0 ± 0.8* (−5%)	56.0 ± 0.7** (−8%)	58.0 ± 0.2* (−5%)
Cholinesterase (U/L)	1,348.8 ± 41.1	870.0 ± 32.7*** (−35%)	900.9 ± 46.9*** (−33%)	993.8 ± 87.2* (−26%)
AST (U/L)	73.0 ± 4.6	108.7 ± 2.6*** (+49%)	184.1 ± 30.3** (+152%)	115.3 ± 8.6** (+58%)
ALT (U/L)	35.0 ± 1.5	44.3 ± 5.0 (+27%)	46.8 ± 4.4* (+34%)	39.0 ± 2.9 (+11%)

[a]Laham et al. (1991).
[b]Results expressed as mean ± SEM (percent change compared with control) for 4–6 rats/ group; % change control = [(treatment mean – control mean)/control mean] × 100.
[c]HEC_{ER} = (ppm × MW ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × ratio of blood:gas partition coefficient (animal:human) [default value of 1].
*Statistically significantly different from control ($p < 0.05$), as reported by the study authors.
**Statistically significantly different from control ($p \leq 0.01$), as reported by the study authors.
***Statistically significantly different from control ($p < 0.001$), as reported by the study authors.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODEL-FITTING PROCEDURE FOR CANCER INCIDENCE DATA

The model-fitting procedure for dichotomous cancer incidence is as follows. The Multistage-Cancer Model in the EPA's benchmark dose software (BMDS) (Version 2.6) is fit to the incidence data using the extra risk option. The multistage-cancer model is run for all polynomial degrees up to $n-1$ (where n is the number of dose groups including control). An adequate model fit is judged by three criteria: (1) goodness-of-fit p-value ($p < 0.1$), (2) visual inspection of the dose-response curve, and (3) scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the benchmark dose lower confidence limit (BMDL) for the best fitting multistage-cancer model as judged by the goodness-of-fit p-value and Akaike's information criterion (AIC) is selected as the point of departure (POD). In accordance with U.S. EPA (2012b) guidance, benchmark dose (BMD) and BMDL values associated with an extra risk of 10% are calculated.

BMD MODELING TO IDENTIFY POTENTIAL PODs FOR p-OSF DERIVATION

The following data set was selected for BMD modeling:

- Incidence data for forestomach squamous cell papilloma in female B6C3F$_1$ mice administered benzaldehyde via gavage 5 days/week for 104 weeks (NTP, 1990).

Increased Incidence of Forestomach Squamous Cell Papilloma in Female Mice Exposed to Benzaldehyde for 104 Weeks

The procedure outlined above was applied to the data for forestomach squamous cell papilloma in female B6C3F$_1$ mice administered benzaldehyde via gavage 5 days/week for 104 weeks (NTP, 1990) (see Table C-1). Table C-2 summarizes the BMD modeling results. Both multistage cancer models provided adequate fit to the incidence data, with the 2-degree multistage cancer model converging upon the 1-degree. Thus, the BMDL$_{10HED}$ of 25.7 mg/kg-day from the 1-degree model is selected for this end point (see Figure C-1 and the BMD text output for details).

Table C-1. Combined Incidence of Forestomach Squamous Cell Papilloma in Female B6C3F$_1$ Mice Administered Benzaldehyde via Gavage 5 Days/Week for 104 Weeks[a]

	HED (mg/kg-d)[b]		
	0	**30.0**	**60.1**
Sample size	50	50	50
Incidence	0	5	6

[a]NTP (1990).
[b]Gavage doses were converted to ADDs by multiplying the administered gavage dose by (5/7) days/week and converted into HEDs using BW$^{3/4}$ scaling.

Table C-2. BMD Modeling Results for Incidence of Forestomach Squamous Cell Papilloma in Female B6C3F$_1$ Mice Administered Benzaldehyde via Gavage 5 Days/Week for 104 Weeks

Model	χ^2 Goodness-of-Fit *p*-value[a]	Scaled Residuals[b]	AIC	BMD_{10} (mg/kg-d, HED)	$BMDL_{10}$ (mg/kg-d, HED)
Multistage-cancer (1-degree)[c,d]	0.7076	0.675	71.8645	40.61	25.67
Multistage-cancer (2-degree)[c]	0.7076	0.675	71.8645	40.61	25.67

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals for dose group close to the BMD.
[c]Power restricted to ≥1.
[d]Selected model.

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

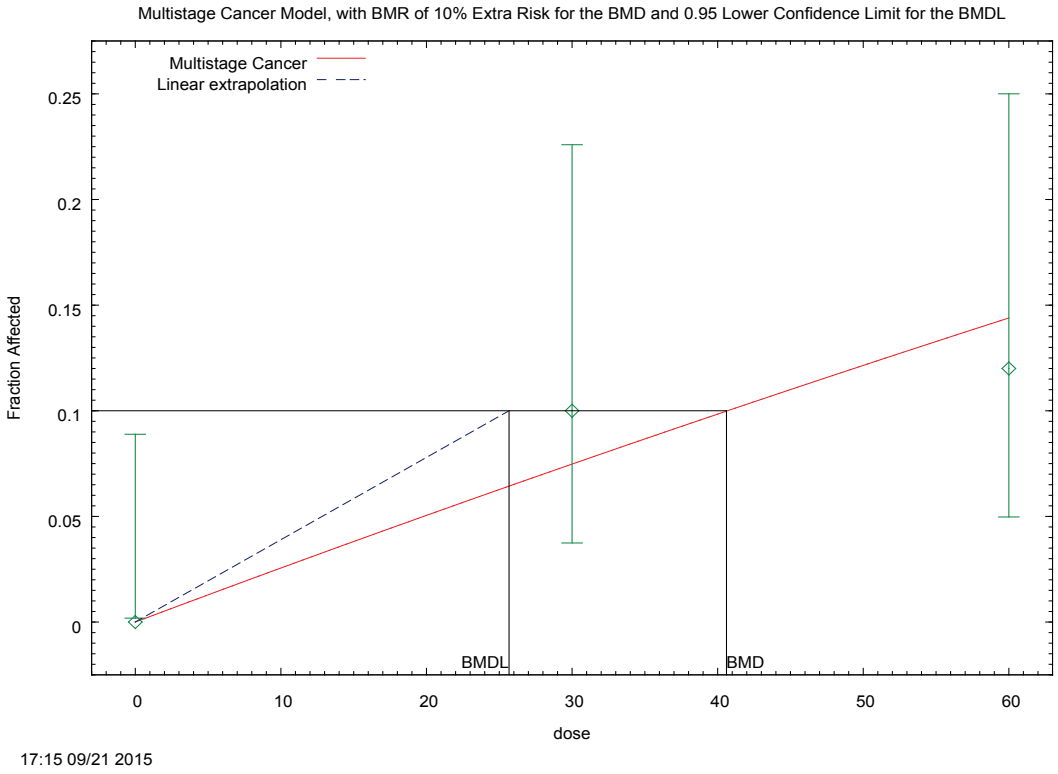

Figure C-1. Multistage (1-degree) Model for Incidence of Forestomach Squamous Cell Papilloma in Female B6C3F$_1$ Mice Administered Benzaldehyde via Gavage 5 Days/Week for 104 Weeks (NTP, 1990).

Text Output for Multistage (1-degree) Model for Incidence of Forestomach Squamous Cell Papilloma in Female B6C3F$_1$ Mice Administered Benzaldehyde via Gavage 5 Days/Week for 104 Weeks (NTP, 1990)

```
 ================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File: E:/PPRTV/clearance review/Benzaldehyde/Dan
BMD/msc_Benzaldehyde Cancer_Msc1-BMR10.(d)
        Gnuplot Plotting File:  E:/PPRTV/clearance review/Benzaldehyde/Dan
BMD/msc_Benzaldehyde Cancer_Msc1-BMR10.plt
                                                Mon Sep 21 17:15:47 2015
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1


 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =    0.0137196
                        Beta(1) =   0.00213056


           Asymptotic Correlation Matrix of Parameter Estimates

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

                Beta(1)

   Beta(1)            1



                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
```

```
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     Background                0              NA
        Beta(1)       0.00259473      0.000782862          0.00106035
0.00412911

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


                       Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -34.6004         3
   Fitted model         -34.9323         1      0.663714      2          0.7176
  Reduced model         -39.3266         1       9.45234      2         0.00886

           AIC:          71.8645


                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000      50.000        0.000
   30.0000     0.0749         3.744     5.000      50.000        0.675
   60.0000     0.1442         7.209     6.000      50.000       -0.487

 Chi^2 = 0.69      d.f. = 2        P-value = 0.7076


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        40.6055

             BMDL =        25.6719

             BMDU =        74.7426

Taken together, (25.6719, 74.7426) is a 90     % two-sided confidence
interval for the BMD

Cancer Slope Factor =    0.00389531
```

APPENDIX D. REFERENCES

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