

# Provisional Peer-Reviewed Toxicity Values for

## Vinyl Bromide (CASRN 593-60-2)



# Provisional Peer-Reviewed Toxicity Values for

## Vinyl Bromide

(CASRN 593-60-2)

Center for Public Health and Environmental Assessment  
Office of Research and Development  
U.S. Environmental Protection Agency  
Cincinnati, OH 45268

## **AUTHORS, CONTRIBUTORS, AND REVIEWERS**

### **CHEMICAL MANAGER**

J. Phillip Kaiser, PhD, DABT  
Center for Public Health and Environmental Assessment, Cincinnati, OH

### **DRAFT DOCUMENT PREPARED BY**

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

### **PRIMARY INTERNAL REVIEWERS**

Allen Davis, MSPH  
Center for Public Health and Environmental Assessment, Washington, DC

Deborah Segal, MS  
Center for Public Health and Environmental Assessment, Washington, DC

This document was externally peer reviewed under contract to:

Eastern Research Group, Inc.  
110 Hartwell Avenue  
Lexington, MA 02421-3136

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development's (ORD's) CPHEA website at <https://www.epa.gov/pprtv/forms/contact-us-about-pprtvs>.

## TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS AND ACRONYMS .....	v
BACKGROUND .....	1
QUALITY ASSURANCE .....	1
DISCLAIMERS .....	2
QUESTIONS REGARDING PPRTVs .....	2
INTRODUCTION .....	3
REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER) .....	7
HUMAN STUDIES .....	12
ANIMAL STUDIES .....	12
Oral Exposures .....	12
Inhalation Exposures .....	12
OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS) .....	18
Genotoxicity Studies .....	18
Supporting Animal Toxicity Studies .....	23
Absorption, Distribution, Metabolism, and Excretion (ADME) Studies .....	31
Mode-of-Action/Mechanistic Studies .....	32
DERIVATION OF PROVISIONAL VALUES .....	34
DERIVATION OF ORAL REFERENCE DOSES .....	34
DERIVATION OF INHALATION REFERENCE CONCENTRATIONS .....	34
Derivation of Subchronic Provisional Reference Concentration .....	34
Derivation of Chronic Provisional Reference Concentration .....	37
CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR .....	38
MODE-OF-ACTION DISCUSSION .....	39
Hypothesis .....	39
Mode-of-Action Conclusions .....	41
DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES .....	41
Derivation of Provisional Oral Slope Factor .....	41
Derivation of Provisional Inhalation Unit Risk .....	41
APPENDIX A. SCREENING PROVISIONAL VALUES .....	44
APPENDIX B. DATA TABLES .....	45
APPENDIX C. BENCHMARK DOSE MODELING RESULTS .....	58
APPENDIX D. REFERENCES .....	98

## COMMONLY USED ABBREVIATIONS AND ACRONYMS

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

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV document.

## PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR VINYL BROMIDE (CASRN 593-60-2)

### 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.

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.

Currently available PPRTV assessments can be accessed on the U.S. Environmental Protection Agency's (EPA's) PPRTV website at <https://www.epa.gov/pprtv>. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing adverse human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA Superfund and Technology Liaison (<https://www.epa.gov/research/fact-sheets-regional-science>).

### QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two Center for Public Health and Environmental Assessment (CPHEA) scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

## **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. 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 content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) CPHEA website at <https://www.epa.gov/pprtv/forms/contact-us-about-pprtvs>.

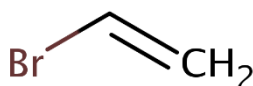
## INTRODUCTION

Vinyl bromide (CASRN 593-60-2) belongs to the halogenated olefin class of compounds ([NTP, 2016](#)). It is primarily used in polymer and copolymer production. Vinyl bromide is also used in pharmaceutical and fumigant production ([NTP, 2016](#); [Belpoggi et al., 2012](#); [HSDB, 2009](#)). It is listed on the U.S. EPA's Toxic Substances Control Act (TSCA) public inventory ([U.S. EPA, 2018b](#)) and is registered with Europe's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) program ([ECHA, 2018](#)).

Vinyl bromide is produced by hydrogen bromide addition to acetylene in the presence of mercury and/or copper halide catalysts. It may also be produced by partial debromination of 1,2-dibromoethane with alcoholic potassium hydroxide ([Belpoggi et al., 2012](#)). Vinyl bromide may be formed in air as a degradation product of 1,2-dibromoethane ([HSDB, 2009](#)).

The empirical formula for vinyl bromide is  $C_2H_3Br$ ; its structure is shown in Figure 1. Table 1 summarizes the physicochemical properties of vinyl bromide. It is a flammable, colorless gas and a liquid below 15.8°C. Although secondary sources [e.g., [NTP \(2017\)](#); [Belpoggi et al. \(2012\)](#); [IARC \(2008\)](#)] have reported that vinyl bromide is insoluble in water, no study details are available to substantiate this reported insolubility. In contrast to those reports, the water solubility of vinyl bromide is estimated to be high at 1.82 mol/L ([U.S. EPA, 2012c](#)) based on a measured log  $K_{ow}$  of 1.57 and water solubility data for analogous chemicals, including bromoethane, vinyl chloride, and chloroethane, with experimental water solubility values of 9, 8.8, and 6.7 g/L, respectively ([ChemIDplus, 2018a, b, c](#)). In the air, vinyl bromide will exist in the gas phase, based on its vapor pressure of 1,033 mm Hg. It will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals and have a half-life of 2.4 days, calculated from a measured reaction rate constant of  $6.8 \times 10^{-12}$  cm<sup>3</sup>/molecule-second at 25°C ([HSDB, 2009](#)). Reaction of vinyl bromide with ozone in the atmosphere is expected to occur more slowly, based on an estimated rate constant of  $2.5 \times 10^{-19}$  cm<sup>3</sup>/molecule-second at 25°C, corresponding to a half-life of 47 days. Volatilization of vinyl bromide from dry soil surfaces is expected based on its vapor pressure. Volatilization from water or moist soil surfaces is expected based on an estimated Henry's law constant of  $7.26 \times 10^{-3}$  atm-m<sup>3</sup>/mole. The estimated  $K_{oc}$  of 31.2 L/kg for vinyl bromide indicates the potential for mobility in soil and a negligible potential to adsorb to suspended solids and sediment in aquatic environments. Hydrolysis of vinyl bromide is not expected because it lacks hydrolysable functional groups ([HSDB, 2009](#)). The compound will polymerize rapidly in sunlight and react vigorously in the presence of oxidizing materials ([Belpoggi et al., 2012](#)). Furthermore, the blood-air partition coefficients determined for vinyl bromide in humans and rats are 2.27 and 4.05 ([Gargas et al., 1989](#)), respectively, which are important for understanding regional deposition/absorption of this chemical and for dosimetry conversions (see section on "Animal Studies" for more details).





**Figure 1. Vinyl Bromide (CASRN 593-60-2) Structure**

<b>Table 1. Physicochemical Properties of Vinyl Bromide (CASRN 593-60-2)</b>	
<b>Property (unit)</b>	<b>Value</b>
Physical state	Colorless gas (>15.8°C) or liquid (<15.8°C) <sup>a</sup>
Boiling point (°C)	15.8 <sup>a</sup>
Melting point (°C)	-137.8 <sup>a</sup>
Density (g/cm <sup>3</sup> at 20°C)	1.4933 <sup>a</sup>
Vapor pressure (mm Hg at 25°C)	1,033 <sup>a</sup>
pH (unitless)	NA
pKa (unitless)	NA
Solubility in water (mol/L at 25°C)	1.82 (predicted average) <sup>b</sup>
Octanol-water partition constant (log K <sub>ow</sub> )	1.57 <sup>a</sup>
Henry's law constant (atm-m <sup>3</sup> /mol at 20°C)	7.26 × 10 <sup>-3</sup> (predicted average) <sup>b</sup>
Soil adsorption coefficient K <sub>oc</sub> (L/kg)	31.2 (predicted average) <sup>b</sup>
Atmospheric OH rate constant (cm <sup>3</sup> /molecule-sec at 25°C)	6.8 × 10 <sup>-12</sup> <sup>a</sup>
Atmospheric half-life (d)	2.4 (calculated based on its measured OH rate constant) <sup>a</sup>
Relative vapor density (air = 1)	3.7 <sup>a</sup>
Molecular weight (g/mol)	106.94 <sup>a</sup>
Flash point (°C)	5 <sup>c</sup>

<sup>a</sup>[HSDB \(2009\)](#).

<sup>b</sup>Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (vinyl bromide; CASRN 593-60-2; <https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID8021432>. Accessed July 15, 2020).

<sup>c</sup>[Belpoggi et al. \(2012\)](#).

NA = not applicable.

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

Table 2. Summary of Available Toxicity Values for Vinyl Bromide (CASRN 593-60-2)			
Source (parameter) <sup>a, b</sup>	Value (applicability)	Notes	Reference <sup>c</sup>
<b>Noncancer</b>			
IRIS (RfC)	0.003 mg/m <sup>3</sup>	Based on hypertrophy and basophilic and eosinophilic foci in the liver in a chronic inhalation study in rats	<a href="#">U.S. EPA (2003)</a>
HEAST (sRfC)	0.003 mg/m <sup>3</sup>	The chronic RfC was adopted as the subchronic RfC; based on hypertrophy and basophilic and eosinophilic foci in the liver in a chronic intermittent inhalation exposure study in rats	<a href="#">U.S. EPA (2011)</a>
DWSHA	NV	NA	<a href="#">U.S. EPA (2012a)</a>
ATSDR	NV	NA	<a href="#">ATSDR (2017)</a>
IPCS	NV	NA	<a href="#">IPCS (2018)</a>
CalEPA	NV	NA	<a href="#">CalEPA (2016)</a> ; <a href="#">CalEPA (2017)</a> ; <a href="#">CalEPA (2018)</a>
OSHA	NV	NA	<a href="#">OSHA (2017a)</a> ; <a href="#">OSHA (2017b)</a>
<b>Cancer</b>			
IRIS	NV	NA	<a href="#">U.S. EPA (2018a)</a>
HEAST (IUR)	0.000032 (μg/m <sup>3</sup> ) <sup>-1</sup>	Based on liver tumors in a chronic intermittent inhalation exposure study in rats	<a href="#">U.S. EPA (2011)</a> ; <a href="#">U.S. EPA (1984)</a>
HEAST (OSF)	0.11 (mg/kg-d) <sup>-1</sup>	Based on liver tumors in a chronic intermittent inhalation exposure study in rats	<a href="#">U.S. EPA (2011)</a> ; <a href="#">U.S. EPA (1984)</a>
DWSHA	NV	NA	<a href="#">U.S. EPA (2012a)</a>
NTP (WOE)	Reasonably anticipated to be a human carcinogen	Based on sufficient evidence of carcinogenicity from studies in experimental animals	<a href="#">NTP (2016)</a>
IARC (WOE)	Group 2A: Probably carcinogenic to humans	Based on inadequate evidence for carcinogenicity in humans, and sufficient evidence in experimental animals, as well as similarity to vinyl chloride	<a href="#">IARC (2008)</a> ; <a href="#">IARC (2017)</a>
CalEPA (WOE)	Listed as causing cancer under Proposition 65	NA	<a href="#">CalEPA (2017)</a> ; <a href="#">CalEPA (2018)</a>
ACGIH (TLV-TWA)	2.2 mg/m <sup>3</sup>	Based on liver cancer	<a href="#">ACGIH (2001)</a> ; <a href="#">ACGIH (2016)</a>

<b>Table 2. Summary of Available Toxicity Values for Vinyl Bromide (CASRN 593-60-2)</b>			
<b>Source (parameter)<sup>a, b</sup></b>	<b>Value (applicability)</b>	<b>Notes</b>	<b>Reference<sup>c</sup></b>
ACGIH (WOE)	A2: Suspected human carcinogen	Based on evidence in animal studies and analogy to vinyl chloride	<a href="#">ACGIH (2001)</a> ; <a href="#">ACGIH (2016)</a>
NIOSH (WOE)	Potential occupational carcinogen	NA	<a href="#">NIOSH (2016)</a>

<sup>a</sup>Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration.

<sup>b</sup>Parameters: IUR = inhalation unit risk; OSF = oral slope factor; RfC = reference concentration; sRfC = subchronic reference concentration; TLV = threshold limit value; TWA = time-weighted average; WOE = weight of evidence.

<sup>c</sup>Reference date for the IRIS cancer data is the date the online source was accessed. All other reference dates are the publication date for the databases.

NA = not applicable; NV = not available.

Non-date-limited literature searches were initially conducted in October 2017 and updated in December 2019 and June 2020 for studies relevant to the derivation of provisional toxicity values for vinyl bromide (CASRN 593-60-2). Searches were conducted by U.S. EPA's Health and Environmental Research Online (HERO) staff and stored in the HERO database.<sup>1</sup> HERO searches the following databases: PubMed, TOXLINE (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), U.S. EPA Chemical Data Access Tool (CDAT), U.S. EPA ChemView, U.S. EPA Health Effects Assessment Summary Tables (HEAST), U.S. EPA Integrated Risk Information System (IRIS), U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), Japan Existing Chemical Data Base (JECDB), National Institute for Occupational Safety and Health (NIOSH), National Toxicology Program (NTP), Organisation for Economic Co-operation and Development (OECD) Existing Chemicals Database, OECD Screening Information Data Set (SIDS) High Production Volume (HPV) Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

<sup>1</sup>U.S. EPA's HERO database provides access to the scientific literature behind U.S. EPA science assessments. The database includes more than 2,500,000 scientific references and data from the peer-reviewed literature used by U.S. EPA to develop reports that support critical agency decision-making for developing its regulations.

## **REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)**

Tables 3A and 3B provide overviews of the relevant noncancer and cancer evidence bases, respectively, for vinyl bromide, and include all potentially relevant repeated short-term, subchronic, and chronic studies, as well as reproductive and developmental toxicity studies. Principal studies used in the PPRTV assessment for derivation of provisional toxicity values are identified in bold. The phrase “statistical significance” and term “significant,” used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3A. Summary of Potentially Relevant Noncancer Data for Vinyl Bromide (CASRN 593-60-2)							
Category <sup>a</sup>	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry <sup>b</sup>	Critical Effects	NOAEL <sup>b</sup>	LOAEL <sup>b</sup>	Reference (comments)	Notes <sup>c</sup>
<b>Human</b>							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m <sup>3</sup> )							
ND							
<b>Animal</b>							
1. Oral (mg/kg-d)							
ND							
2. Inhalation (mg/m <sup>3</sup> )							
Short term	5–10 M, Wistar rat; 7 hr/d, 5 d/wk; 3 d, 1 wk, 2 wk, or 4 wk  Reported analytical concentrations: 0 or 43,763 mg/m <sup>3</sup>	0, 9,117.3	Clinical signs of toxicity (hypoactivity, lethargy) and decreased body weight.	NDr	9,117.3	<a href="#">Leong and Torkelson (1970)</a> ; <a href="#">Dow Chemical (1969)</a>	PR
Short term	5 M/5 F, Charles River rat, 7 hr/d, 5 d/wk, 3 wk  Reported analytical concentrations: 0, 256.3, or 486.1 ppm	0, 233.5, 442.9	No adverse effects.	442.9	NDr	<a href="#">Leong and Torkelson (1970)</a> ; <a href="#">Hazleton Laboratories (1967)</a> [interim sacrifice group]	PR
Subchronic	2–3 M/3–4 F, cynomolgus monkey, 7 hr/d, 5 d/wk, 6 mo  Reported analytical concentrations: 0, 256.3, or 486.1 ppm	0, 233.5, 442.9	Decreased body weight in males and increased absolute and relative liver weight in females.	NDr	233.5	<a href="#">Leong and Torkelson (1970)</a> ; <a href="#">Hazleton Laboratories (1967)</a>	PR, PS

**Table 3A. Summary of Potentially Relevant Noncancer Data for Vinyl Bromide (CASRN 593-60-2)**

Category <sup>a</sup>	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry <sup>b</sup>	Critical Effects	NOAEL <sup>b</sup>	LOAEL <sup>b</sup>	Reference (comments)	Notes <sup>c</sup>
Chronic	25 M/25 F, Charles River rat, 7 hr/d, 5 d/wk, 6 mo  Reported analytical concentrations: 0, 256.3, or 486.1 ppm	0, 233.5, 442.9	No effects.	442.9	NDr	<a href="#">Leong and Torkelson (1970)</a> ; <a href="#">Hazleton Laboratories (1967)</a>	PR
Chronic	3 M/3 F, NZW rabbit, 7 hr/d, 5 d/wk, 6 mo  Reported analytical concentrations: 0, 256.3, or 486.1 ppm	0, 233.5, 442.9	Increased absolute liver weight in males. Decreased body weight and increased relative liver and kidney weight in females.	NDr	233.5	<a href="#">Leong and Torkelson (1970)</a> ; <a href="#">Hazleton Laboratories (1967)</a>	PR
Chronic	120–144 M/120–144 F, S-D rat, 6 hr/d, 5 d/wk, 24 mo  Reported analytical concentrations: 0, 9.7, 52, 247, or 1,235 ppm	0, 7.5, 41, 193, 964.6	Increased incidence of non-neoplastic hepatic lesions (peliosis, eosinophilic foci, basophilic foci). Additional effects at higher exposures included increased hepatocyte hypertrophy, microcytic anemia, hematuria, decreased body weight, and increased mortality.	NDr	7.5	<a href="#">Benya et al. (1982)</a> ; <a href="#">EPL (1978)</a> ; <a href="#">Ethyl Corporation (1979)</a> ; <a href="#">Huntingdon Research Center (1979)</a> ; <a href="#">Dorato (1978)</a>	PR, IRIS

**Table 3A. Summary of Potentially Relevant Noncancer Data for Vinyl Bromide (CASRN 593-60-2)**

Category <sup>a</sup>	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry <sup>b</sup>	Critical Effects	NOAEL <sup>b</sup>	LOAEL <sup>b</sup>	Reference (comments)	Notes <sup>c</sup>
Reproductive/ Developmental	ND						

<sup>a</sup>Duration categories are defined as follows: Acute = exposure for ≤24 hours; short term = repeated exposure for 24 hours to ≤30 days; long term (subchronic) = repeated exposure for >30 days ≤10% lifespan for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% lifespan for humans (>~90 days to 2 years in typically used laboratory animal species) ([U.S. EPA, 2002](#)).

<sup>b</sup>Dosimetry: HECs are calculated for systemic (ER) effects. The HEC values for ER effects were calculated by treating vinyl bromide as a Category 3 gas and using the following equation from [U.S. EPA \(1994\)](#) methodology:  $HEC_{ER} = \text{exposure level (mg/m}^3) \times (\text{hours/day exposed} \div 24 \text{ hours}) \times (\text{days/week exposed} \div 7 \text{ days}) \times \text{ratio of blood-gas partition coefficient (animal:human)}$ , using a default coefficient of 1. The default value was used because the blood-air partition coefficients for monkeys and rabbits are unknown and the rat blood-air partition coefficient of 4.05 is greater than the human blood-air partition coefficient of 2.27 as indicated by [Gargas et al. \(1989\)](#).

<sup>c</sup>Notes: IRIS = used by [U.S. EPA \(2003\)](#); PR = peer reviewed; PS = principal study.

ER = extrarespiratory; F = female(s); HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; ND<sub>r</sub> = not determined; NOAEL = no-observed-adverse-effect level; NZW = New Zealand White; S-D = Sprague-Dawley.

Table 3B. Summary of Potentially Relevant Cancer Data for Vinyl Bromide (CASRN 593-60-2)					
Category	Number of Male/Female, Strain, Species, Study Type, Reported Doses, Study Duration	Dosimetry <sup>a</sup>	Critical Effects	Reference (comments)	Notes <sup>b</sup>
<b>Human</b>					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m <sup>3</sup> )					
ND					
<b>Animal</b>					
1. Oral (mg/kg-d)					
ND					
2. Inhalation (mg/m <sup>3</sup> )					
Carcinogenicity	120–144 M/120–144 F, S-D rat, 6 hr/d, 5 d/wk, 24 mo  Reported analytical concentrations: 0, 9.7, 52, 247, or 1,235 ppm	0, 7.5, 41, 193, 964.6	Significant increase in the incidence of angiosarcomas (primarily in liver) in males and females at $\geq 7.5$ mg/m <sup>3</sup> ; exposure-related tumors observed at higher exposures included hepatocellular neoplasms (combined), and Zymbal gland squamous cell carcinoma and papilloma.	<a href="#">Benya et al. (1982)</a> ; <a href="#">Ethyl Corporation (1979)</a> ; <a href="#">Dorato (1978)</a> ; <a href="#">EPL (1978)</a> ; <a href="#">Huntingdon Research Center (1979)</a>	PR, PS

<sup>a</sup>Dosimetry: Inhalation exposure units are expressed as HECs (mg/m<sup>3</sup>). The HEC for ER effects was calculated by treating vinyl bromide as a Category 3 gas and using the following equation from [U.S. EPA \(1994\)](#) methodology:  $HEC_{ER} = \text{exposure level (mg/m}^3) \times (\text{hours/day exposed} \div 24 \text{ hours}) \times (\text{days/week exposed} \div 7 \text{ days}) \times \text{ratio of blood-gas partition coefficient (animal:human)}$ , using a default coefficient of 1 because the rat blood-air partition coefficient of 4.05 is greater than the human blood-air partition coefficient of 2.27 as indicated by [Gargas et al. \(1989\)](#).

<sup>b</sup>Notes: PR = peer reviewed; PS = principal study.

ER = extrarrespiratory; F = female(s); HEC = human equivalent concentrations; M = male(s); ND = no data; S-D = Sprague-Dawley.



## HUMAN STUDIES

No studies have been identified that evaluated potential health effects in humans following exposure to vinyl bromide. [IARC \(1986\)](#) reported that exposure to high vapor concentrations of vinyl bromide can cause unconsciousness; however, no specific source for this information was cited.

## ANIMAL STUDIES

### Oral Exposures

No repeated-dose oral studies have been identified.

### Inhalation Exposures

#### *Short-Term Studies*

[Leong and Torkelson \(1970\)](#); [Dow Chemical \(1969\)](#)

Groups of Wistar rats (five males/group) were exposed to vinyl bromide (purity 99.7%) at a mean analytical vapor concentration of 43,763 mg/m<sup>3</sup> for 7 hours/day, 5 days/week for 3 days, 1 week, 2 weeks, or 4 weeks via whole-body inhalation. Results are available in both a published paper by [Leong and Torkelson \(1970\)](#) and an unpublished report by [Dow Chemical \(1969\)](#). An additional group of 10 male rats served as sham controls, with exposure to filtered room air under similar conditions for 4 weeks. Food and water were provided ad libitum except during exposure periods. The rats were observed daily for mortality and clinical signs of toxicity. Body weights were measured 3 times/week. All animals were sacrificed at the end of the assigned exposure period and examined for gross and histopathological changes in “major organs” (not further defined). Control rats were sacrificed with the final exposure group. Reported statistical analyses were limited to Student’s *t*-test for body-weight data.

One exposed rat was sacrificed moribund on the Exposure Day 9 due to respiratory distress; all other rats survived until the scheduled sacrifice. Exposed rats showed decreased activity during the first hour of exposure each day, with drowsiness and inactivity for the remaining 6 hours of daily exposure. Clinical signs were rapidly reversed upon removal from the exposure chamber. Body weights in exposed rats were significantly and progressively decreased by 9 and 11% after 15 and 20 exposures, respectively, compared with control (see Table B-1). At scheduled necropsy, the study authors reported that no exposure-related gross or histopathological lesions were observed in major organs (no quantitative data were reported). Multifocal gray areas were observed in the lung of the rat that was sacrificed moribund; however, no histopathological lung lesions were observed. The study authors reported that all other major organs were considered normal at necropsy in this animal.

The only exposure level of 43,763 mg/m<sup>3</sup> (HEC = 9,117.3 mg/m<sup>3</sup>) is identified as a lowest-observed-adverse-effect level (LOAEL) based on clinical signs of toxicity (hypoactivity, lethargy) and decreased body weight. The analytical concentration of 43,763 mg/m<sup>3</sup> corresponds to a human equivalent concentration (HEC) value of 9,117.3 mg/m<sup>3</sup> for extrarrespiratory effects.<sup>2</sup>

---

<sup>2</sup>HEC for extrarrespiratory effects calculated by treating vinyl bromide as a Category 3 gas and using the following equation from [U.S. EPA \(1994\)](#) methodology:  $HEC_{ER} = \text{exposure level (mg/m}^3\text{)} \times (\text{hours/day exposed} \div 24 \text{ hours}) \times (\text{days/week exposed} \div 7 \text{ days}) \times \text{ratio of blood-gas partition coefficient (animal:human)}$ , using a default coefficient of 1 because the rat blood-air partition coefficient of 4.05 is greater than the human blood-air partition coefficient of 2.27 as indicated by [Gargas et al. \(1989\)](#).

***Subchronic and Chronic Studies with Interim Sacrifice***

*Leong and Torkelson (1970); Hazleton Laboratories (1967)*

The results of a 6-month inhalation study of vinyl bromide in rats, monkeys, and rabbits are described in an unpublished industry report by [Hazleton Laboratories \(1967\)](#) and a peer-reviewed publication by [Leong and Torkelson \(1970\)](#). The rat study included a 3-week interim sacrifice group.

Groups of Charles River rats (25/sex/group), cynomolgus monkeys (3/sex/group), and New Zealand White rabbits (3/sex/group) were exposed to vinyl bromide (purity 99.7%) at analytical vapor concentrations (mean  $\pm$  standard deviation [SD]) of  $256.3 \pm 39.4$  ppm ( $1,121 \pm 172$  mg/m<sup>3</sup>) or  $486.1 \pm 58.3$  ppm ( $2,126 \pm 255$  mg/m<sup>3</sup>),<sup>3</sup> for 7 hours/day, 5 days/week for 6 months via whole-body inhalation. The control animals (2 male and 4 female monkeys, 3 rabbits/sex, 25 rats/sex) were exposed to filtered room air under the same conditions. Additional groups of rats (5 rats/sex/group) were similarly exposed to vinyl bromide and sacrificed after 3 weeks (interim sacrifice group). Food and water were provided ad libitum except during exposure periods. The animals were observed daily for mortality and clinical signs of toxicity. Body weights were recorded weekly in rats and rabbits, but only before and after the 6-month exposure period in monkeys. Weekly food consumption was determined 1 week prior to exposure and during the first and sixth month of exposure in five rats/sex/group and in all rabbits; food consumption was not monitored in monkeys. Hematological parameters were evaluated prior to exposure and after 2, 10, and 24 weeks of exposure to 0 or 2,126 mg/m<sup>3</sup> in all monkeys, five rats/sex/group, and all rabbits. Additionally, hematological parameters were measured in five rats/sex/group exposed to 0 or 1,121 mg/m<sup>3</sup> prior to exposure and after 24 weeks of exposure. Hematological endpoints included red blood cell (RBC) count, white blood cell (WBC) count, and differential hemoglobin (Hb) and hematocrit (Hct). At sacrifice, all animals were subjected to gross necropsy, and the lungs, heart, liver, spleen, kidneys, and gonads were removed and weighed. These organs, along with the thyroid, pancreas, and adrenals, were examined microscopically. Nasal tissues were not examined for gross or histopathological changes. Reported statistical analyses were limited to analysis of variance (ANOVA) for body and -organ-weight data.

Nine rats died during the study, but the deaths were attributed to accidental injuries and distributed across exposure groups (one male control, two males at 1,121 mg/m<sup>3</sup>, two males at 2,126 mg/m<sup>3</sup>, two female controls, and two females at 1,121 mg/m<sup>3</sup>). No clinical signs of toxicity, body-weight effects, or changes in food consumption were reported. No exposure-related hematological changes were observed. At the 3-week interim sacrifice, significant organ-weight changes included an 18% decrease in absolute kidney weight in females at 2,126 mg/m<sup>3</sup> and a 1.6- to 3-fold increase in relative ovary weight in females at  $\geq 1,121$  mg/m<sup>3</sup> (see Table B-2). However, at the 6-month terminal sacrifice, exposure-related changes were not observed in the kidney or ovary (see Table B-3). Significant organ-weight changes at 6 months were limited to the low-exposure group, including increases of 13 to 17% in relative heart weight in males and females, respectively, and increases of 9 and 12% in absolute and relative liver weight, respectively, in males (see Table B-3). Because of inconsistencies in findings and lack of associated histopathological lesions, the study authors considered these organ-weight changes

---

<sup>3</sup>Concentration in mg/m<sup>3</sup> = concentration in ppm  $\times$  molecular weight (106.94 g/mol)  $\div$  24.45 L/mol.

incidental. No exposure-related lesions were observed in any organ evaluated at 3 weeks, or 6 months.

All monkeys survived until scheduled sacrifice, and no clinical signs of toxicity were observed. Terminal body weights in males were decreased by 25% at 2,126 mg/m<sup>3</sup>, compared with control (see Table B-4). Terminal body weight in females was biologically significantly decreased at 1,121 mg/m<sup>3</sup> but not at 2,126 mg/m<sup>3</sup> (see Table B-4; note that a  $\geq 10\%$  decrease in body weight is considered to be biologically significant by the U.S. EPA for the purposes of this PPRTV assessment). No exposure-related changes in hematological parameters were seen. Some variation was noted in organ weights at terminal sacrifice, including slight increases in relative liver weights in males at 2,126 mg/m<sup>3</sup>, increases in relative spleen weights in both sexes at  $\geq 1,121$  mg/m<sup>3</sup>, and decreases in relative thyroid weights in males at 2,126 mg/m<sup>3</sup> and females at  $\geq 1,121$  mg/m<sup>3</sup> (see Table B-4); however, these findings were not statistically or biologically significant. Conversely, both absolute and relative liver weights were biologically significantly increased in females at  $\geq 1,121$  mg/m<sup>3</sup> (note that a  $\geq 10\%$  increase in absolute and relative liver and kidney weight is considered biologically significant by the U.S. EPA for the purposes of this PPRTV assessment). No exposure-related lesions were reported in any of the organs evaluated.

All rabbits survived until scheduled sacrifice. An infestation of ear mites occurred in the colony during Study Week 16 and was treated by applying castor oil to the ears. Some animals in all groups had transient diarrhea due to incidental ingestion of the castor oil. No exposure-related hematological changes were observed. In male rabbits, relative liver and kidney weights were biologically significantly increased at 1,121 mg/m<sup>3</sup> but not at 2,126 mg/m<sup>3</sup>, and absolute liver weight was biologically significantly increased at  $\geq 1,121$  mg/m<sup>3</sup>. In female rabbits, body weight was biologically significantly decreased ( $\geq 10\%$ ) at  $\geq 1,121$  mg/m<sup>3</sup>. Relative liver weight was biologically significantly increased ( $\geq 10\%$ ) at 2,126 mg/m<sup>3</sup>. Relative kidney weight was biologically significantly increased ( $\geq 10\%$ ) at  $\geq 1,121$  mg/m<sup>3</sup>. No exposure-related changes in organ histology were observed in any organ evaluated.

In rats, the highest exposure level of 2,126 mg/m<sup>3</sup> (HEC = 442.9 mg/m<sup>3</sup>) is a NOAEL based on a lack of clearly adverse, statistically significant findings. In monkeys, the lowest concentration of 1,121 mg/m<sup>3</sup> (HEC = 233.5 mg/m<sup>3</sup>) is identified as a LOAEL for increased absolute and relative liver weights in females. In rabbits, a LOAEL of 1,121 mg/m<sup>3</sup> (HEC = 233.5 mg/m<sup>3</sup>) is identified based on decreased body weight and increased relative kidney weight in females and increased absolute liver weight in males. The analytical concentrations of 1,121 and 2,126 mg/m<sup>3</sup> correspond to HEC values of 233.5 and 442.9 mg/m<sup>3</sup>, respectively, for systemic (extrarespiratory) effects.<sup>4</sup>

---

<sup>4</sup>HEC for extrarespiratory effects calculated by treating vinyl bromide as a Category 3 gas and using the following equation from [U.S. EPA \(1994\)](#) methodology:  $HEC_{ER} = \text{exposure level (mg/m}^3\text{)} \times (\text{hours/day exposed} \div 24 \text{ hours}) \times (\text{days/week exposed} \div 7 \text{ days}) \times \text{ratio of blood-gas partition coefficient (animal:human)}$ , using a default coefficient of 1 because the monkey and rabbit blood-air partition coefficients for vinyl bromide are not known, and the rat blood-air partition coefficient of 4.05 is greater than the human blood-air partition coefficient of 2.27 as indicated by [Gargas et al. \(1989\)](#).

***Chronic/Carcinogenicity Study with Interim Sacrifices***

*Benya et al. (1982); Dorato (1978); EPL (1978); Huntingdon Research Center (1979); Ethyl Corporation (1979)*

Results of a chronic 2-year inhalation bioassay in rats, along with 6-, 12-, and 18-month interim sacrifices, were reported in a peer-reviewed study by [Benya et al. \(1982\)](#). A series of unpublished industry reports ([Ethyl Corporation, 1979](#); [Huntingdon Research Center, 1979](#); [Dorato, 1978](#); [EPL, 1978](#)) also provide interim sacrifice data and pathology reports. In this study ([Benya et al., 1982](#)), groups of Sprague-Dawley (S-D) rats (120/sex/group) were exposed to vinyl bromide (purity 99.9%) at analytical concentrations (mean  $\pm$  SD) of  $9.7 \pm 1.5$  ppm ( $42 \pm 6.6$  mg/m<sup>3</sup>),  $52 \pm 5$  ppm ( $230 \pm 20$  mg/m<sup>3</sup>),  $247 \pm 13$  ppm ( $1,080 \pm 57$  mg/m<sup>3</sup>), or  $1,235 \pm 102$  ppm ( $5,402 \pm 446$  mg/m<sup>3</sup>)<sup>5</sup> for 6 hours/day, 5 days/week for up to 24 months via whole-body inhalation. The control group (144 rats/sex) was similarly exposed to filtered and conditioned outside air. Five rats/sex/group were sacrificed at 6 months, 10 rats/sex/group were sacrificed at 12 and 18 months, and all remaining rats were scheduled for sacrifice at 24 months. Food was available ad libitum except during exposure periods, and water was available ad libitum at all times. The animals were observed daily for mortality and clinical signs of toxicity. Body weights were recorded weekly. Blood was collected at each interim and terminal sacrifice for clinical chemistry (glucose, blood urea nitrogen [BUN], alkaline phosphatase [ALP], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], protein, bilirubin, albumin, cholesterol, calcium, phosphate) and hematology (WBC count, RBC count, Hb, Hct, mean corpuscular volume [MCV]). Urine was collected at 6, 12, and 18 months for urinalysis (bilirubin, occult blood, pH, glucose, ketones, proteins, specific gravity). Prior to exposure, 10 rats/sex/group were evaluated for baseline hematologic, clinical chemistry, and urinalysis measurements. All animals, including any animal that died or was sacrificed moribund, were subject to gross necropsy. The adrenal glands, brain, gonads, kidneys, liver, heart, lungs, trachea, pituitary, spleen, and thyroids were removed and weighed. A complete set of 30 organs and tissues was examined for histopathological changes at each interim and terminal sacrifice from all exposure groups. In all rats that died or were sacrificed moribund, the lungs, liver, Zymbal gland, mammary gland, brain, and gross lesions were examined microscopically. Statistical analyses included Kruskal-Wallis one-way ANOVA followed by Mann-Whitney U test for nonparametric continuous data, Bartlett's test followed by Student's *t*-test for parametric continuous data, and Yates-corrected  $\chi^2$  test for dichotomous data.

Mortality was increased in a concentration-related manner at exposures  $\geq 230$  mg/m<sup>3</sup> after approximately 12 months of exposure. Based on graphically reported data, mortality at 12 months (not including planned interim sacrifices) was approximately 12% in male and female rats exposed to 5,402 mg/m<sup>3</sup>, and  $<10\%$  in all other groups. At 18 months, the estimated cumulative unplanned mortality based on graphically reported data was 8–12, 6–13, 15–19, 24–42, and 66–77% in rats exposed to 0, 42, 230, 1,080, and 5,402 mg/m<sup>3</sup>, respectively. Because of the high mortality at 5,402 mg/m<sup>3</sup>, all surviving rats from this group were sacrificed at 18 months. Mortality in other groups was approximately 40–42, 45–47, 68–82, and 94–95% at 24-month terminal sacrifice in rats exposed to 0, 42, 230, and 1,080 mg/m<sup>3</sup>, respectively (estimated from graphically reported data).

No clinical signs of toxicity aside from mortality were reported. Based on graphically reported data, body weights were similar to controls throughout the first year of the study in all

<sup>5</sup>Concentration in mg/m<sup>3</sup> = concentration in ppm  $\times$  molecular weight (106.94 g/mol)  $\div$  24.45 L/mol.

groups, but decreased over the course of the second year such that terminal body weights (18 months at 5,402 mg/m<sup>3</sup> and 24 months in the other groups) were decreased by approximately 10–20% at exposure levels  $\geq 230$  mg/m<sup>3</sup>. No significant concentration-related, body-weight changes were observed at the 6- or 12-month interim sacrifices (see Tables B-5 and B-6); data for the 18-month interim sacrifice were not available. Significant hematological findings at 18 months included decreases of 12–34% in Hct in females at  $\geq 1,080$  mg/m<sup>3</sup> and males at 5,402 mg/m<sup>3</sup>, decreases of 25–27% in Hb and RBC count in females at 5,402 mg/m<sup>3</sup>, and decreases of 6–10% in MCV in males and females at  $\geq 1,080$  mg/m<sup>3</sup> (see Tables B-7 and B-8). The study authors considered the findings to be suggestive of microcytic anemia at 5,402 mg/m<sup>3</sup>. Sporadic significant hematological findings were also observed at 6 and 12 months (see Tables B-7 and B-8). Small, but statistically significant, changes were observed in clinical chemistry data at 6, 12, and 18 months; however, no clear patterns with respect to concentration, time, or direction of change were observed (see Tables B-9 and B-10). Urinalysis showed hematuria at 18 months in male and female rats exposed at 5,402 mg/m<sup>3</sup>; no other altered urinalysis parameters were observed (data not shown by the study authors). No hematological, clinical chemistry, or urinalysis data were presented following terminal sacrifice at 24 months for groups exposed to concentrations up to 1,080 mg/m<sup>3</sup> (all rats exposed to 5,402 mg/m<sup>3</sup> were sacrificed at 18 months).

The study authors qualitatively reported elevated liver weights at  $\geq 1,080$  mg/m<sup>3</sup> and elevated kidney weights at 5,402 mg/m<sup>3</sup> after 18–24 months of exposure; however, quantitative data, the sex of animals affected, the magnitude of change, and statistical significance of these findings were not reported by [Benya et al. \(1982\)](#). None of the unpublished interim reports contain these data, but [Huntingdon Research Center \(1979\)](#) reported organ-weight data for the 6- and 12-month interim sacrifices (see Tables B-5 and B-6). The study authors reported significant increases of 21–39% in relative liver weight in males at 42–1,080 mg/m<sup>3</sup> at 6 months, and 16% at 5,402 mg/m<sup>3</sup> at 12 months. Elevated absolute liver weights were also observed; however, the study authors did not report statistics for absolute organ weights. Based on statistics conducted for this review, absolute liver weights in males were significantly increased by 18–46% at 230–1,080 mg/m<sup>3</sup> at 6 months, and 26% at 5,402 mg/m<sup>3</sup> at 12 months. Liver weights in exposed females did not differ significantly from control. Based on available data, liver-weights do not display consistent time- and concentration-related changes. Sporadic significant changes were observed in the kidney and spleen weights of the exposed rats, compared with control; however, findings were not consistent between sexes or time points and did not show exposure-related patterns (see Tables B-5 and B-6).

[Benya et al. \(1982\)](#) did not report non-neoplastic microscopic findings. However, non-neoplastic data are available from unpublished reports describing this study ([Ethyl Corporation, 1979](#); [Huntingdon Research Center, 1979](#); [EPL, 1978](#)). Various non-neoplastic liver lesions were observed in the exposed animals. The study authors indicated that exposure-related findings in animals treated for  $\geq 18$  months included hepatocyte hypertrophy, eosinophilic and basophilic foci, and peliosis; however, the observed lesions differed between sexes and time points (see Tables B-11 and B-12). Statistics were not reported for non-neoplastic lesions but were conducted for this review. Significant findings at 18 months included increased incidence of focal hepatocyte hypertrophy in males and females at  $\geq 230$  mg/m<sup>3</sup>, basophilic foci in males at  $\geq 230$  mg/m<sup>3</sup>, eosinophilic foci in males at 230 mg/m<sup>3</sup>, and peliosis in males at 230 and 1,080 mg/m<sup>3</sup> and in females at 42 mg/m<sup>3</sup>. At 24 months, significant findings included increased incidence of eosinophilic and basophilic foci in males at



42 and 230 mg/m<sup>3</sup> and basophilic foci at 42 mg/m<sup>3</sup> in females, compared with controls. These lesions were first observed in unscheduled deaths that occurred between 6 and 12 months, and low incidences were observed at the 12-month interim sacrifice (see Tables B-11 and B-12) ([Huntingdon Research Center, 1979](#)). No exposure-related non-neoplastic lesions were observed at the 6-month interim sacrifice ([Huntingdon Research Center, 1979](#)). The study authors attributed the lack of consistent significant non-neoplastic hepatic findings at the higher exposure levels to increased incidence of neoplastic liver lesions (see Table B-13), including hepatic angiosarcoma, hepatocellular carcinoma, and hepatic neoplastic nodules. All rats exposed to 5,402 mg/m<sup>3</sup> showed increased mortality and were sacrificed early. The study authors' conclusion is supported by the fact that the NTP often considers basophilic and eosinophilic foci as preneoplastic ([Maronpot, 2016](#)). At  $\geq 230$  mg/m<sup>3</sup>, peliosis was also observed in males, and focal hepatocyte hypertrophy was observed in males and females after exposure for 18–24 months. Additional effects reported at  $\geq 1,080$  mg/m<sup>3</sup> included increased mortality, decreased body weight, microcytic anemia, and hematuria. The analytical concentrations of 42, 230, 1,080, and 5,402 mg/m<sup>3</sup> correspond to HEC values of 7.5, 41, 193, and 964.6 mg/m<sup>3</sup>, respectively, for systemic (extrarespiratory) effects.<sup>6</sup>

A LOAEL of 42 mg/m<sup>3</sup> (HEC = 7.5 mg/m<sup>3</sup>) is identified based on increased incidence of non-neoplastic hepatic lesions after exposure for 18–24 months, including eosinophilic foci in males, basophilic foci in males and females, and peliosis in females. No NOAEL is identified.

Exposure-related neoplastic tumors were observed in all treated groups. Table B-13 shows the tumor data for all animals combined, including data at terminal and interim sacrifices and the number of animals found dead or sacrificed moribund. Neoplasms were first observed in unscheduled deaths that occurred between the 6- and 12-month interim sacrifice at  $\geq 1,080$  mg/m<sup>3</sup>, with low incidences observed at  $\geq 42$  mg/m<sup>3</sup> at the 18-month interim sacrifice. The most common tumors were angiosarcomas, which had a significantly increased incidence in male and female rats from all exposure groups. These tumors occurred primarily in the liver, but were observed occasionally in the lung, spleen, nasal cavity, and mesentery. Hepatocellular carcinoma and neoplastic nodules (combined) were also increased in females at 42 mg/m<sup>3</sup> and in males and females at 1,080 mg/m<sup>3</sup>. The tumor incidences at 5,402 mg/m<sup>3</sup> were not significantly elevated in either sex, but the study authors attributed this to early mortality and the high incidence of hepatic angiosarcoma in this group. In the Zymbal gland, the incidence of squamous cell carcinoma was significantly increased in males at  $\geq 1,080$  mg/m<sup>3</sup> and in females at 5,402 mg/m<sup>3</sup>. Zymbal gland papilloma incidence was significantly increased in males at 5,402 mg/m<sup>3</sup> only. Other neoplastic observations were similar between the exposed and control animals.

### ***Reproductive/Developmental Studies***

No reproductive or developmental toxicity studies have been identified.

---

<sup>6</sup>HEC for extrarespiratory effects calculated by treating vinyl bromide as a Category 3 gas and using the following equation from [U.S. EPA \(1994\)](#) methodology:  $HEC_{ER} = \text{exposure level (mg/m}^3\text{)} \times (\text{hours/day exposed} \div 24 \text{ hours}) \times (\text{days/week exposed} \div 7 \text{ days}) \times \text{ratio of blood-gas partition coefficient (animal:human)}$ , using a default coefficient of 1 because the rat blood-air partition coefficient of 4.05 is greater than the human blood-air partition coefficient of 2.27 as indicated by [Gargas et al. \(1989\)](#).

## OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

### Genotoxicity Studies

Available genotoxicity studies are shown in Table 4A and reviewed below. Studies consistently show that vinyl bromide and/or its metabolites are mutagenic in bacterial and invertebrate systems and have the potential to cause chromosomal damage. Data in mammalian species are extremely limited but indicate that vinyl bromide can directly interact with deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).

Vinyl bromide is mutagenic to *Salmonella typhimurium* both with and without metabolic activation ([NTP, 2017](#); [Wagner et al., 1992](#); [Roldán-Arjona et al., 1991](#); [Lijinsky and Andrews, 1980](#); [Bartsch et al., 1979a](#)). Vinyl bromide also induces sex-linked recessive lethal mutations, DNA repair, chromosomal alterations (CAs), and mitotic recombination in *Drosophila melanogaster* ([Ballering et al., 1996](#); [Vogel and Nivard, 1993](#); [Roldán-Arjona et al., 1991](#)). Studies in mammals are limited but showed evidence of DNA damage in multiple organs in mice following oral exposure ([Sasaki et al., 1998](#)) and DNA and RNA adduct formation by reactive metabolites following in vitro or in vivo exposure ([Guengerich, 1981](#); [Laib et al., 1980](#); [Ottenwälder et al., 1979](#)).

**Table 4A. Summary of Vinyl Bromide Genotoxicity**

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation <sup>a</sup>	Results with Activation <sup>a</sup>	Comments	References
<b>Genotoxicity studies in prokaryotic organisms</b>						
Reverse mutation	<i>Salmonella typhimurium</i> TA100, TA1530	0, 0.2, 2, 20% (v/v in air)	+	+	Plate test (gas exposure); increase in revertants/plate was >threefold at all exposure levels with or without metabolic activation. No cytotoxicity was observed.	<a href="#">Bartsch et al. (1979a)</a>
Reverse mutation	<i>S. typhimurium</i> TA100, TA1535	0, 1, 5, 10%	+	+	Plate test (gas exposure); increase in revertants/plate was >twofold at ≥5%, both with and without metabolic activation in TA100 (quantitative results not reported for TA1535).	<a href="#">Lijinsky and Andrews (1980)</a>
Reverse mutation	<i>S. typhimurium</i> TA98, TA100	0, 0.001, 0.002, 0.007, 0.013, 0.02, 1 µg/plate	+ (TA100)  - (TA98)	+	Plate test (gas exposure); increase in revertants/plate was >twofold at all exposure levels in TA100, with or without activation and in TA98 with activation. Slight cytotoxicity observed at ≥0.02 µg/plate.	<a href="#">NTP (2017)</a> [unpublished]
Reverse mutation	<i>S. typhimurium</i> TA100	NR	+	+	Desiccator gas-phase exposure (inverted plate). Mutagenic with and without metabolic activation.	<a href="#">Wagner et al. (1992)</a> [abstract only]
Forward mutation	<i>S. typhimurium</i> BA12, BAL12	142 × 10 <sup>3</sup> nmol/mL	+	+	Ara assay; alternative assay used liquid test with fixed dose with varying durations (0–120 min).	<a href="#">Roldán-Arjona et al. (1991)</a>



**Table 4A. Summary of Vinyl Bromide Genotoxicity**

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation <sup>a</sup>	Results with Activation <sup>a</sup>	Comments	References
<b>Genotoxicity studies—acellular systems in vitro</b>						
DNA binding	Calf liver DNA	NR	NA	+	DNA adduct formation was observed. Coincubation with epoxide hydrolase decreased binding by ~50%; no change was observed with coincubation with dehydrogenases. These results indicate that 2-bromoethylene oxide is the predominant DNA-binding metabolite and 2-bromoacetaldehyde is the preferred metabolite for protein binding.	<a href="#">Guengerich (1981)</a>
RNA binding	Calf liver RNA	NR	NA	+	Gas phase all-glass incubation system; <sup>14</sup> C-labeled vinyl bromide was used. RNA alkylation products were detected, including radioactive ethenoadenosine and ethenocytidine (adduct formation).	<a href="#">Ottenwälder et al. (1979)</a>
<b>Genotoxicity studies—mammalian species in vivo</b>						
DNA damage (comet assay)	Male CD-1 mice were exposed to vinyl bromide via a single gavage dose in olive oil. Mice were sacrificed at 0 (zero-time control), 3, and 24 hr after treatment. At sacrifice, stomach, liver, kidney, urinary bladder, lung, brain, and bone marrow were removed and analyzed for DNA damage.	0, 2,000 mg/kg	+ (stomach, liver, kidney, urinary bladder, lung, brain)  – (bone marrow)	NA	Migration of nuclear DNA was significantly elevated at 3 and/or 24 hr after exposure in all organs except bone marrow. No deaths, morbidity, clinical signs, or gross or microscopic lesions in evaluated organs were observed.	<a href="#">Sasaki et al. (1998)</a>

**Table 4A. Summary of Vinyl Bromide Genotoxicity**

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation <sup>a</sup>	Results with Activation <sup>a</sup>	Comments	References
RNA binding	Rats (strain and sex) were exposed to <sup>14</sup> C-labeled vinyl bromide via inhalation for 8 hr; rats were sacrificed after exposure; liver RNA was evaluated for RNA alkylation.	0, 20, 200 ppm	+	NA	A new protein band was identified in mRNA analysis, indicating alkylation of RNA species (adduct formation).	<a href="#">Laib et al. (1980)</a> [abstract only]
RNA binding	Male Wister rats (number not specified) were exposed to <sup>14</sup> C-labeled vinyl bromide via inhalation for 8 hr; rats were sacrificed after exposure; liver RNA was evaluated for RNA alkylation.	0, 250 ppm	+	NA	RNA alkylation products were detected in liver samples of exposed animals, including radioactive ethenoadenosine and ethenocytidine (adduct formation).	<a href="#">Ottenwälder et al. (1979)</a>
<b>Genotoxicity studies—vertebrates in vivo</b>						
Sex-linked recessive lethal with DNA repair assay	<i>Drosophila melanogaster</i> ( <i>mus201 ext-</i> [repair deficient] and <i>mei9 ext+</i> [repair proficient] genotypes) were evaluated. Adult males were exposed via inhalation for 48 hr and then mated with unexposed females.	0, 54,000 ppm	+	NA	Induction of recessive lethals in both genotypes. Enhanced mutation ratio ( <i>exr-/exr+</i> ) indicates that some DNA modifications are reparable.	<a href="#">Ballerig et al. (1996)</a>

**Table 4A. Summary of Vinyl Bromide Genotoxicity**

Endpoint	Test System	Doses/Concentrations Tested	Results without Activation <sup>a</sup>	Results with Activation <sup>a</sup>	Comments	References
CA (ring X-chromosome loss)	<i>D. melanogaster</i> ring-X ( <i>R(1)2yB:B<sup>S</sup>Y<sup>+</sup></i> ) males were exposed via inhalation for 48 hr and then mated with unexposed females ( <i>u w spl sn<sup>3</sup>: bw sp<sup>2</sup></i> ). The F <sub>1</sub> progeny were scored for CAs.	0, 14,500 ppm	+	NA	CAs were significantly induced. The calculated I <sub>CL/RL</sub> index of 2.4 indicated that vinyl bromide is a highly clastogenic agent (CL:RL ratio <1 is nonactive, CL:RL ratio >2 is highly clastogenic agent).	<a href="#">Ballerling et al. (1996)</a>
Mitotic recombination (w/w <sup>+</sup> eye mosaic bioassay)	<i>D. melanogaster</i> (four wild-type strains [BK, OK, LS, 91-C] and 2 DDT-resistant strains [HK, HG]) were evaluated. Progeny of mated pairs (50 pairs/group) were exposed via inhalation for 17 hr.	0, 2,000, 4,000, 8,000, 16,000, 24,000 ppm	+ (91-C, HG, HK)  ± (LS, BK, OK)	NA	Induction rates were 91-C ≥ HG ~HK > BK ~LS ~OK. A 60-fold difference in induction was observed between the highest induction rate (91-C) and the lowest (OK). Differences were attributed to different levels of bioactivation across strains. The highest exposure level (24,000 ppm) was toxic.	<a href="#">Roldán-Arjona et al. (1991)</a>
Mitotic recombination (w/w <sup>+</sup> eye mosaic bioassay)	<i>D. melanogaster</i> larvae (18–52 hr old; LS wild-type strain) were exposed to vinyl bromide via inhalation for 17 hr.	0, 4,000, 8,000, 32,000, 64,000, 128,000 ppm	+	NA	Results were considered marginally positive or inconclusive at 4,000–32,000 ppm (1.5- to 3.4-fold induction), and positive at 64,000 ppm (10-fold induction). The highest exposure level (128,000 ppm) was lethal.	<a href="#">Vogel and Nivard (1993)</a>

<sup>a</sup>+ = positive; ± = weakly positive; - = negative.

Ara = L-Arabinose resistance; CA = chromosomal aberration; CL = chromosome loss; DDT = dichlorodiphenyltrichloroethane; DNA = deoxyribonucleic acid; ICL/RL = rate of induced chromosome loss over the recessive lethal rate; mRNA = messenger ribonucleic acid; NA = not applicable; NR = not reported; RL = recessive lethal; RNA = ribonucleic acid.

### **Supporting Animal Toxicity Studies**

Numerous acute toxicity studies were identified, including studies by oral, inhalation, and dermal exposure routes. These studies primarily focused on mortality and clinical signs of toxicity; however, a limited number of studies on hepatotoxicity were also identified. Additionally, supporting studies for carcinogenic effects in animals include a briefly reported neonatal inhalation study evaluating the development of preneoplastic foci in rat livers, a dermal skin tumor bioassay, and a subcutaneous tumor bioassay. Supporting studies are shown in Table 4B and are briefly reviewed below.

Table 4B. Other Studies				
Test	Materials and Methods	Results	Conclusions	References
<b>Supporting evidence—noncancer effects in animals following oral exposure</b>				
Acute (oral)	Rats (2/group; sex and strain unspecified) were exposed to 500, 1,000, or 2,000 mg/kg via a single gavage dose in corn oil. Endpoints evaluated included mortality and clinical signs.	Both animals given 2,000 mg/kg died within minutes and had severe GI tract distention. Both animals given 1,000 mg/kg died within 3 hr (no additional details reported). One animal given 500 mg/kg died in 2 d; both animals had diarrhea and bleeding from the nose.	The lowest exposure level of 500 mg/kg is an apparent FEL for mortality.	<a href="#">Dow Chemical (1990)</a> [unpublished]
Acute (oral)	Male CD-1 mice (4/group) were exposed to 2,000 mg/kg via a single gavage dose in olive oil. Mice were sacrificed at 0 (zero-time control), 3, and 24 hr after treatment. Endpoints evaluated included mortality, clinical signs, and gross and microscopic examination of stomach, liver, kidney, urinary bladder, lung, or brain.	No exposure-related toxicity findings.	The only administered dose of 2,000 mg/kg is an apparent NOAEL for evaluated endpoints.	<a href="#">Sasaki et al. (1998)</a>
<b>Supporting evidence—noncancer effects in animals following inhalation exposure</b>				
Acute (inhalation)	The ALC, or the concentration at which mortality was first observed following a 4-hr exposure, was determined in rats. No further details were provided.	Vinyl bromide was classified as having low toxicity (ALC value of >5,000 ppm).	Rat ALC (4-hr) = 30,000 ppm (131,000 mg/m <sup>3</sup> ).	<a href="#">Kennedy and Graepel (1991)</a>
Acute (inhalation)	Rats (3–5/group; sex and strain unspecified) were exposed to vinyl bromide vapor concentrations of 25,000 ppm for 7 hr, 50,000 ppm for 1.25 or 6.75 hr, or 100,000 ppm for 10 or 15 min. Endpoints examined included clinical signs and mortality.	All rats exposed to 100,000 ppm for 15 min, or 50,000 ppm for 6.75 hr become unconscious after 3 and 25 min, respectively; all animals died. Rats exposed to 25,000 ppm for 7 hr, 50,000 ppm for 1.25 hr, or 100,000 ppm for 10 min were also anesthetized, but regained consciousness after exposure ceased. At necropsy, lung, liver, and kidney injuries (unspecified) were observed in dead and surviving animals exposed to ≥50,000 ppm.	The lowest concentration of 25,000 ppm (109,300 mg/m <sup>3</sup> ) is identified as a LOAEL for anesthetic effects. Lethality was observed at ≥50,000 ppm (218,700 mg/m <sup>3</sup> ).	<a href="#">Dow Chemical (1990)</a> [unpublished]

**Table 4B. Other Studies**

Test	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	White mice (10–40/group) were exposed once to vinyl bromide vapor at three, or more, unspecified concentrations for 10 min. Endpoints examined were anesthesia and mortality.	The minimal certain anesthetic concentration was 3.5 mM/L (370,000 mg/m <sup>3</sup> ), and the highest tolerated (nonlethal) concentration was 7.0 mM/L (740,000 mg/m <sup>3</sup> ).	The concentration of 3.5 mM/L (370,000 mg/m <sup>3</sup> ) is identified as a LOAEL for anesthetic effects. Data reporting was inadequate to identify a NOAEL.	<a href="#">Abreu et al. (1939)</a>
Acute/short term (inhalation)	Male rats (species and number unspecified) were exposed to 20,000 ppm vinyl bromide vapor via inhalation for 5 hr/d for 1, 2, 5, or 10 consecutive d. Additional groups received either phenobarbital or potassium bromide in drinking water during exposure to vinyl bromide. Endpoints evaluated included clinical signs, body weight, food intake, and hepatic injury (not specified). It is unclear whether an unexposed control group was included.	CNS depression, decreased body weight, and decreased food intake were observed in rats exposed to vinyl bromide alone during the first few d of exposure. Decreased food intake, and subsequent body-weight decrease, was attributed to CNS depression. “Toxic injury to the liver” was observed on D 1 and 2, but not 5 and 10. Serum bromide levels were elevated. Based on findings from rats exposed to phenobarbital or potassium bromide, elevated serum bromide was due to vinyl bromide debromination, not ingestion of bromide from drinking water.	The only concentration of 20,000 ppm (87,500 mg/m <sup>3</sup> ) is an apparent LOAEL for CNS depression and liver injury; however, methods and data reporting are inadequate for independent review.	<a href="#">Vanstee et al. (1977)</a> [abstract]
Acute (inhalation)	Twenty white mice were exposed once to vinyl bromide vapor at 2.5 mM/L for 60 min. Forty unexposed white mice served as controls. Endpoints examined were mortality, anesthesia, and liver bromide levels.	2.5 mM/L (270,000 mg/m <sup>3</sup> ) was established as an anesthetic concentration. It is unclear whether any mice died because mortality data were combined for 10 compounds (21/200 anesthetized mice died). Inorganic bromide levels in the liver were increased by 2.7-fold in exposed mice compared with unexposed controls.	The only exposure concentration of 2.5 mM/L (270,000 mg/m <sup>3</sup> ) is identified as a LOAEL for anesthetic effects.	<a href="#">Abreu and Emerson (1940)</a>

**Table 4B. Other Studies**

Test	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	Male Holtzman rats (3–5/group) were exposed to vinyl bromide vapor at 11,000, 21,000, 33,000, or 51,000 ppm for 4 hr after pretreatment with PCB (300 µM via gavage for 3 d prior to vinyl bromide exposure). Controls were unexposed or treated with PCB only. Endpoints evaluated included mortality, clinical signs, SAKT, and liver weight. Based on reported findings, groups of rats (number unspecified) were similarly exposed to 0 or 20,000 ppm vinyl bromide after pretreatment with PCB for examination of liver histology. The study authors also indicated that additional groups were exposed to vinyl bromide without PCB pretreatment and evaluated for all endpoints, but details regarding exposure level and animal number were not reported.	<p>One rat exposed to 51,000 ppm + PCB died; no other mortalities were observed. Clinical signs of toxicity (e.g., prostration) were observed at 51,000 ppm + PCB. Significant differences in hepatic endpoints between PCB-only controls, and PCB + vinyl bromide exposure groups included a 20-fold increase in SAKT at 33,000 ppm and 20–65% increases in relative liver weights at all exposure levels. A similar pattern was observed when PCB + vinyl bromide exposure groups were compared with unexposed controls (statistics not reported). No differences in these endpoints were observed between rats exposed to vinyl bromide alone and unexposed controls.</p> <p>Histological changes in the liver of rats exposed to vinyl bromide + PCB included severe midzonal to centrilobular necrosis and hemorrhagic areas at 20,000 ppm. In PCB-only rats, histological changes were limited to midzonal and centrilobular cytoplasmic vacuolization and some eosinophilic foci. No histopathological changes were observed in unexposed controls or rats exposed to vinyl bromide alone.</p>	Results indicate that metabolism of vinyl bromide (induced by pretreatment with PCB) produces a hepatotoxic compound, presumably a reactive epoxide.	<a href="#">Conolly et al. (1978)</a>

**Table 4B. Other Studies**

Test	Materials and Methods	Results	Conclusions	References
Acute (inhalation)	Male Holtzman rats (3–6/group) were exposed to vinyl bromide vapor at 10,000 ppm for 4 hr after pretreatment with PCB (300 µM via gavage for 3 d prior to exposure) with or without exposure to the epoxide hydrolase inhibitor, TCPE (1 mL/kg via gavage immediately before vinyl bromide exposure). Half of the rats were fasted overnight prior to exposure. Controls were exposed to PCB + TCPE only. The study did not include an unexposed control or vinyl bromide-only exposure group. Endpoints evaluated included mortality and serum SDH.	Observed mortality was 1/6 of the fed rats and 3/6 of the fasted rats exposed to vinyl bromide + PCB + TCPE. SDH levels were significantly elevated by 20-fold in fasted rats exposed to vinyl bromide + PCB, compared with fed rats exposed to vinyl bromide + PCB. Increased toxicity with fasting was attributed to depletion of GSH in PCB-treated rats. There was no significant difference in fed or fasted rats exposed to vinyl bromide + PCB + TCPE, compared with fed or fasted rats exposed to vinyl bromide + PCB only. However, the study authors suggested that TCPE findings may have been confounded by elevated mortality.	Results indicate that metabolism of vinyl bromide (induced by pretreatment with PCB) produces a hepatotoxic compound that is detoxified via GSH conjugation. However, the lack of proper controls limits the conclusions that can be made from this study.	<a href="#">Conolly and Jaeger (1977)</a>
Acute (inhalation)	Rats (1–2/group; sex and strain unspecified) were exposed once to vinyl bromide vapor concentrations of 10,000, 50,000, 80,000, or 100,000 ppm for 10–60 min. Endpoints examined included clinical signs and mortality.	One rat died after a 10-min exposure to 100,000 ppm, another rat survived a 15-min exposure to the same concentration. Rats exposed to concentrations up to 80,000 ppm for up 15–60 min survived.	The exposure level of 100,000 ppm (437,000 mg/m <sup>3</sup> ) is an apparent FEL for mortality. Study design, low animal number, and limited reporting preclude identification of a NOAEL.	<a href="#">Dow Chemical (1938)</a> [unpublished]
<b>Supporting evidence—noncancer effects in animals following exposure via other routes</b>				
Acute (dermal)	Undiluted liquid vinyl bromide was applied to the belly of rabbits (number unspecified) for 10 d (intact skin) or 3 d (abraded skin) under occluded conditions. The skin was observed daily and for 21 d after exposure.	Slight to moderate redness was observed after 4–10 applications on intact skin; skin was normal at 21 d. For abraded skin, slight redness was observed after each application, then subsided. There was a slight scar at 21 d. No clinical signs of toxicity were observed.	Vinyl bromide is “essentially” nonirritating.	<a href="#">Dow Chemical (1990)</a> [unpublished]
Acute (ocular)	Undiluted liquid vinyl bromide was applied directly to rabbit eyes (number unspecified). Both washed and unwashed protocols were used.	Slight to moderate conjunctivitis with slight swelling was observed. Symptoms resolved within 48 hr.	Vinyl bromide is a moderate eye irritant.	<a href="#">Dow Chemical (1990)</a> [unpublished]



**Table 4B. Other Studies**

Test	Materials and Methods	Results	Conclusions	References
<b>Supporting evidence—cancer effects in animals following exposure via any route</b>				
Carcinogenicity (inhalation)	Newborn Wistar rats (and their dams) were exposed to vinyl bromide vapor at 0 or 2,000 ppm for 8 hr/d, 5 d/wk beginning on the first d of life. The study authors indicated that young rats were sacrificed 2 wk after cessation of exposure, but they reported data for PNW 8, 10, 12, and 15. It is unclear from the report whether these values refer to the number of exposure wk or the wk of sacrifice. Preneoplastic hepatic foci were quantified by counting ATPase-deficient foci.	A time-related increase in the ATPase-deficient hepatocytes was observed from 8 to 15 wk (0.04–0.3%).	Data suggest that vinyl bromide has oncogenic potential in neonatal mouse liver; however, data reporting is too limited for independent review.	<a href="#">Bolt et al. (1979)</a> [letter to the editor]
Carcinogenicity (dermal)	In a complete carcinogenicity assay, 30 female ICR/Ha Swiss mice were dermally exposed to 15 mg liquid vinyl bromide in 0.1 mL acetone, 3 times/wk for 60 wk under nonoccluded conditions. An additional group of 30 females was unexposed (negative control). Skin was evaluated for tumor formation.	No skin tumors were observed.	Vinyl bromide is not carcinogenic under the conditions of this study. (Note: vinyl bromide is volatile, so a substantial portion of the dose may have evaporated.)	<a href="#">Van Duuren (1977)</a>
Carcinogenicity (dermal)	In an initiation/promotion assay, 30 female ICR/Ha Swiss mice were dermally exposed once to 15 mg liquid vinyl bromide in 0.1 mL acetone under nonoccluded conditions, followed by dermal exposure to 2.5 µg TPA in 0.1 mL acetone 3 times/wk for 60 wk. Additional groups (30 females/group) were initiated with DMBA prior to TPA exposure (positive control), exposed to TPA only, or were unexposed (negative control). Skin was evaluated for tumor formation.	Only 1/30 mice exposed to vinyl bromide + TPA developed a skin papilloma at 412 d. One skin carcinoma was observed in the TPA-only group, and no skin tumors were observed in the negative control. A high number of skin tumors was observed in the positive control group.	Vinyl bromide is not a skin tumor initiator under the conditions of this study. (Note: vinyl bromide is volatile, so a substantial portion of the dose may have evaporated.)	<a href="#">Van Duuren (1977)</a>

Table 4B. Other Studies				
Test	Materials and Methods	Results	Conclusions	References
Carcinogenicity (s.c. injection)	Thirty female ICR/Ha Swiss mice were exposed to liquid vinyl bromide via s.c. injection in trioctanoin once weekly for 48 wk at a dose of 25 mg/animal. Additional groups (30/group) were injected with trioctanoin alone or were left untreated. The animals were examined for s.c. tumors for up to 420 d.	No local tumors were observed at the injection site. Other sites were not examined for tumors.	Vinyl bromide is not carcinogenic under the conditions of this study.	<a href="#">Van Duuren (1977)</a>

ALC = approximate lethal concentration; ATPase = adenosine triphosphatase; CNS = central nervous system; DMBA = 7,12-dimethylbenz[a]anthracene; FEL = frank effect level; GI = gastrointestinal; GSH = glutathione; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PCB = polychlorinated biphenyl mixture; PNW = postnatal week; SAKT = serum alanine- $\alpha$ -ketoglutarate transaminase; s.c. = subcutaneous; SDH = sorbitol dehydrogenase; TCPE = trichloropropane epoxide; TPA = 12-*O*-tetradecanoylphorbol 13-acetate.

### ***Supporting Studies for Noncarcinogenic Effects in Animals***

Oral toxicity information is limited to data from two single-exposure studies: one in rats and one in mice. In an unpublished rat study, 1/2, 2/2, and 2/2 rats died following a single gavage exposure to 500, 1,000, or 2,000 mg/kg, respectively ([Dow Chemical, 1990](#)). Death occurred within minutes at the high dose, and the animals had severe gastrointestinal (GI) distention. Diarrhea and bleeding from the nose were observed at lower doses. In the mouse study, no exposure-related changes were observed in stomach, liver, kidney, urinary bladder, lung, or brain histology 3 or 24 hours after a single gavage exposure to 2,000 mg/kg ([Sasaki et al., 1998](#)).

Several studies evaluated mortality and clinical signs following inhalation exposure to vinyl bromide vapor. The approximate lethal concentration (ALC) in rats following a 4-hour inhalation exposure was reported as 30,000 ppm (131,000 mg/m<sup>3</sup>) ([Kennedy and Graepel, 1991](#)). Additional studies reported mortalities in rats at 50,000 ppm (218,700 mg/m<sup>3</sup>) for 6.75 hours or 100,000 ppm (437,000 mg/m<sup>3</sup>) for ≥10 minutes; lung, liver, and kidney injuries (unspecified) were observed in rats exposed to concentrations associated with lethality ([Dow Chemical, 1990](#)). No mortalities were reported in mice exposed to concentrations up to 7.0 mM/L (750,000 mg/m<sup>3</sup>) for 10 minutes ([Abreu et al., 1939](#)). Central nervous system (CNS) depression and anesthetic effects were reported at concentrations as low as 20,000 ppm (87,500 mg/m<sup>3</sup>) in rats ([Dow Chemical, 1990](#); [Vanstee et al., 1977](#)) and 2.5 mM/L (270,000 mg/m<sup>3</sup>) in mice ([Abreu and Emerson, 1940](#); [Abreu et al., 1939](#)).

Two acute inhalation studies focused on hepatic endpoints in rats exposed to vinyl bromide following pretreatment with polychlorinated biphenyl (PCB) mixtures to induce metabolism ([Conolly et al., 1978](#); [Conolly and Jaeger, 1977](#)). [Conolly et al. \(1978\)](#) reported elevated liver weight, histopathological liver lesions (centrilobular necrosis, hemorrhagic areas), and elevated serum alanine-α-ketoglutarate transaminase (SAKT; a marker of hepatic injury) in PCB-pretreated rats exposed to vinyl bromide at concentrations ≥11,000 ppm (48,110 mg/m<sup>3</sup>) for 4 hours, relative to vinyl bromide-only, PCB-only, and untreated controls. Similarly, [Conolly and Jaeger \(1977\)](#) reported elevated sorbitol dehydrogenase (SDH) levels in PCB-pretreated rats exposed to vinyl bromide at a concentration of 10,000 ppm (43,700 mg/m<sup>3</sup>) for 4 hours, but only if they were fasted overnight prior to vinyl bromide exposure. This effect was attributed to glutathione (GSH)-depletion in fasted rats exposed to PCB.

In dermal and ocular irritation studies, liquid vinyl bromide was considered nonirritating to rabbit skin and moderately irritating to rabbit eyes ([Dow Chemical, 1990](#)).

### ***Supporting Studies for Carcinogenic Effects in Animals***

In a letter to the editor, [Bolt et al. \(1979\)](#) reported induction of preneoplastic foci in young rats following neonatal exposure to vinyl bromide or vinyl chloride. Starting on the day of birth, neonates (and their dams) were exposed by inhalation to either vinyl bromide or vinyl chloride at vapor concentrations of 0 or 2,000 ppm (8,750 mg/m<sup>3</sup>) for 8 hours/day, 5 days/week for up to 15 or 17 weeks. The study authors indicated that young rats were sacrificed 2 weeks after cessation of exposure, but reported data for Postnatal Weeks 8, 10, 12, and 15. It is unclear from the report whether these values refer to the number of exposure weeks or the week of sacrifice. Both compounds induced preneoplastic foci at all time points; however, the potency of vinyl bromide was 1/10 that of vinyl chloride.

In a series of carcinogenicity studies, [Van Duuren \(1977\)](#) reported that vinyl bromide did not cause skin tumors alone or as a tumor initiator following dermal exposure, or at the injection site following subcutaneous exposure. Limitations of these studies include lack of evaluation of sites away from the site of exposure, as well as lack of control for volatility of vinyl bromide in the dermal studies.

## Absorption, Distribution, Metabolism, and Excretion (ADME) Studies

### *Absorption*

Reported blood-air partition coefficients in humans and rats are 2.27 and 4.05, respectively ([Gargas et al., 1989](#); [Gargas et al., 1988](#)). Based on the blood-air partition coefficients, vinyl bromide vapor is absorbed from the lungs. No data on the absorption of liquid vinyl bromide following oral exposure were available; however, based on evidence of toxicity in rats following acute oral exposure ([Dow Chemical, 1990](#)), it is presumably absorbed to some degree. Data on the absorption of liquid vinyl bromide following dermal exposure is limited to an estimated human skin permeability coefficient of  $5.5 \times 10^{-3}$  cm/hour ([U.S. EPA, 1992](#)).

### *Distribution*

No in vivo data on distribution following exposure to vinyl bromide are available. However, distribution is expected to be widespread, and the predicted volume of distribution is higher for vinyl bromide than related compounds such as vinyl chloride and vinyl fluoride ([IARC, 1986](#)). Based on a general four-compartment pharmacokinetic model developed for inhaled toxicants with low water solubility, vinyl bromide is expected to rapidly equilibrate between blood and richly perfused tissues ([Andersen et al., 1980](#)). However, vinyl bromide does not equilibrate as quickly between blood and poorly perfused tissues (e.g., adipose), and is therefore expected to accumulate in these tissues ([Andersen et al., 1980](#)). Derived tissue-air partition coefficients in rats (4.05 in blood, 3.33 in liver, 2.26 in muscle, and 49.2 in fat) support these model predictions ([Gargas et al., 1988](#)).

### *Metabolism*

Based on in vitro studies, along with analogy to vinyl chloride, the primary oxidative metabolite of vinyl bromide is bromoethylene oxide ([Guengerich, 1981](#); [Bartsch et al., 1979a](#); [Barbin et al., 1975](#)). Bromoethylene oxide can either be rearranged into 2-bromoacetaldehyde or further metabolized into nonreactive metabolites by epoxide hydrolase and glutathione-S transferase (GST). 2-Bromoacetaldehyde is oxidized to bromoacetic acid, which can also be further metabolized into a nonreactive metabolite by GST ([NTP, 2015](#)). Evidence of irreversible nucleic acid and protein binding following in vitro and/or in vivo exposure support metabolic generation of an alkylating agent ([Guengerich, 1981](#); [Guengerich et al., 1981](#); [Bolt et al., 1978](#); [Barbin et al., 1975](#)). Studies using various metabolic inhibitors have shown that 2-bromoethylene oxide is the primary DNA-binding agent, whereas 2-bromoacetaldehyde preferably binds protein due to its slower DNA-binding kinetics ([Guengerich, 1981](#); [Guengerich et al., 1981](#)). Increased levels of serum and hepatic bromide levels following vinyl bromide exposure also indicate that debromination occurs during metabolism ([Gargas and Andersen, 1982](#); [Vanstee et al., 1977](#); [Leong and Torkelson, 1970](#); [Abreu and Emerson, 1940](#)). Release of bromide is increased following pretreatment with phenobarbital, which induces cytochrome P450 (CYP450) ([Vanstee et al., 1977](#)).

In vitro experiments using isolated liver tissue have shown that hepatocytes metabolize vinyl bromide via CYP450 in rats and mice ([Ottenwälder and Bolt, 1980](#); [Bartsch et al., 1979a](#);

[Bolt et al., 1978](#); [Barbin et al., 1975](#)). In rats, the rate of metabolism was approximately 50% slower in liver microsomes from S-D rats than from Wistar rats ([Bolt et al., 1978](#)). In vitro, vinyl bromide is a substrate for human CYP450 2E1, with a metabolic rate of 0.027 nmol product/minute nmol CYP, with 1,N<sup>6</sup>-ethanoadenosine as the measured product ([Guengerich et al., 1991](#)).

A series of gas uptake studies in rats inferred the metabolism kinetics of vinyl bromide based on the disappearance of vinyl bromide vapor from a recirculated atmosphere ([Gargas and Andersen, 1982](#); [Filser and Bolt, 1981](#); [Andersen et al., 1980](#); [Filser and Bolt, 1979](#)). These studies show that vinyl bromide has saturable uptake kinetics. Because vinyl bromide can readily pass through cell membranes without the aid of carrier proteins, this saturable uptake most likely reflects saturable metabolism ([Andersen et al., 1980](#)). [Filser and Bolt \(1979\)](#) identified a vapor concentration of 55 ppm (240 mg/m<sup>3</sup>) as the saturation point for vinyl bromide in Wistar rats. In Fischer rats, the saturation point has been identified as “well below 100 ppm” (437 mg/m<sup>3</sup>) ([Gargas and Andersen, 1982](#)). Below this saturation point, first-order kinetics applies, and the rate-limiting step is presumably the hepatic perfusion rate. Above this saturation point, zero-order kinetics applies, and metabolic capacity is the rate-limiting step.

### ***Excretion***

Data on excretion are limited; however, unmetabolized vinyl bromide is expected to be eliminated primarily via exhalation ([Andersen, 1980](#)). This is supported by excretion data for vinyl chloride, which indicate that excretion is primarily via exhalation of the unchanged compound at exposure concentrations above metabolic saturation; at lower exposure concentrations, metabolites are primarily excreted via the urine ([U.S. EPA, 2000](#)). [Leong and Torkelson \(1970\)](#) concluded that elimination following inhalation exposure was rapid based on the observed quick recovery of anesthetized animals following cessation of exposure.

### ***Physiologically Based Pharmacokinetic (PBPK) Modeling***

Using a four-compartment pharmacokinetic model for inhaled toxicants with low water solubility developed from gas uptake studies, an inhalation  $K_m$  of 18 ppm and  $V_{max}$  of 2.1 mg/kg-hour were estimated in Fischer rats ([Gargas and Andersen, 1982](#); [Andersen, 1980](#)). However, a three-compartment model based on bromide release into the blood following inhalation exposure predicted two distinct phases, with an estimated  $K_m$  of 33 ppm and  $V_{max}$  of 2.3 mg/kg-hour for low concentrations, and a  $K_m$  of 11,700 ppm and  $V_{max}$  of 9.3 mg/kg-hour for concentrations above saturation ([Gargas and Andersen, 1982](#)). The study authors proposed that the first phase represented a high-affinity metabolic pathway, while the second phase represented a low-affinity metabolic pathway. They attributed the differences in pharmacokinetic constants estimated using the different methods to the low sensitivity of the gas uptake methodology in identifying low affinity pathways.

### **Mode-of-Action/Mechanistic Studies**

Mechanistic studies for non-neoplastic effects are limited. In an abstract, [Vanstee et al. \(1977\)](#) proposed that the observed CNS depression following inhalation exposure to 20,000 ppm (87,500 mg/m<sup>3</sup>) vinyl bromide vapor for 5 hours was in response to observed elevations in serum bromide concentration. Based on a series of experiments in rats following inhalation exposure to vinyl halides (vinyl bromide, vinyl chloride, or vinyl fluoride) under various conditions to alter metabolic function (coexposure to PCB with fasting or the epoxide hydrolase inhibitor,

trichloropropane epoxide), [Conolly and Jaeger \(1977\)](#) proposed that hepatotoxicity of vinyl halides is mediated via epoxide intermediates.

In contrast to non-neoplastic mechanistic studies, the studies on the mode of action (MOA) for carcinogenicity of vinyl bromide are extensive. Data presented below are based on reviews by [NTP \(2016\)](#), [NTP \(2015\)](#), [IARC \(2008\)](#), [ACGIH \(2001\)](#), [IARC \(1999\)](#), and [Solomon \(1999\)](#). A more detailed presentation of this proposed MOA can be found in the “Cancer Weight-of-Evidence Descriptor” section.

Carcinogenicity of vinyl bromide is likely mediated via a genotoxic MOA. As discussed above, vinyl bromide is a direct-acting mutagen and its metabolism produces the DNA, RNA, and protein alkylating agents, bromoethylene oxide, and 2-bromoacetaldehyde. Based on analogy to reactive vinyl chloride metabolites, the major DNA adduct is expected to be 7-(2-oxoethyl)guanosine resulting from interaction with the primary DNA binding agent, bromoethylene oxide. This adduct is considered chemically unstable and can form potentially mutagenic abasic sites following spontaneous depurination. Cyclic ethenodeoxyadenosine and ethenodeoxycytidine RNA adducts have also been observed following exposure to vinyl bromide (and vinyl chloride), and these pro-mutagenic cyclic etheno adducts can result in DNA miscoding by modifying base-pairing sites. Both 2-bromoethylene oxide and 2-bromo-acetaldehyde, have been proposed to react with adenine and cytosine bases to form these etheno-RNA adducts. Compared with 7-(2-oxoethyl)guanosine, etheno adducts have a longer half-life, and thus have a greater capacity to accumulate over time. Therefore, formation of pro-mutagenic etheno adducts is considered the primary key event for tumor formation following exposure to vinyl bromide. While direct evidence for the proposed MOA for vinyl bromide is limited, the proposed MOA is supported by similarities in reactive metabolites, adduct formation, and primary tumor type (hepatic angiosarcoma) to the established human carcinogen, vinyl chloride.



## DERIVATION OF PROVISIONAL VALUES

### DERIVATION OF ORAL REFERENCE DOSES

The oral database is limited to acute studies, precluding derivation of oral reference doses.

### DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

#### Derivation of Subchronic Provisional Reference Concentration

The database of potentially relevant studies for deriving a subchronic reference value for vinyl bromide includes a 4-week study in rats ([Leong and Torkelson, 1970](#); [Dow Chemical, 1969](#)), a 3-week interim study in rats ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)), and a 6-month study in monkeys ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)). The 6-month studies in rats and rabbits were not considered for deriving the subchronic provisional reference concentration (p-RfC) because the durations are greater than 90 days, which is greater than 10% of the life expectancy for rats and rabbits. Therefore, the experiments in rats and rabbits are considered chronic studies and thus not suitable for deriving a subchronic reference value ([U.S. EPA, 2002](#)). Conversely, the duration of the monkey study is less than 10% of the species life expectancy. In the 4-week rat study, the only exposure level of 43,763 mg/m<sup>3</sup> (HEC: 9,117.3 mg/m<sup>3</sup>) was identified as a LOAEL based on clinical signs of toxicity during daily exposures (hypoactivity, lethargy), and decreases in body weight >10% ([Leong and Torkelson, 1970](#); [Dow Chemical, 1969](#)). For the 3-week study in rats, the highest exposure level of 2,126 mg/m<sup>3</sup> (HEC: 442.9 mg/m<sup>3</sup>) was identified as a NOAEL ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)). In the 6-month study in monkeys, the lowest concentration of 1,121 mg/m<sup>3</sup> (HEC: 233.5 mg/m<sup>3</sup>) is identified as a LOAEL for increased absolute and relative liver weights in females.

Based on comparison of the PODs, the most sensitive treatment-related changes from the inhalation toxicity database for vinyl bromide were observed in the 6-month study in monkeys ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)). All available continuous models in the Benchmark Dose Software (BMDS, Version 2.7) were fit to the data sets for the sensitive endpoints presented in Table B-4. Appendix C contains details of the modeling results for these data sets. The HEC, in mg/m<sup>3</sup>, was used as the dose metric. The benchmark response (BMR) for changes in liver or body weight used was a 10% relative deviation (RD) change from control means, which is considered a biologically significant response. For the effects that were considered for modeling (i.e., decreased body weight in males, increased absolute and relative liver weight in females), BMD modeling only provided adequate fit for increased relative liver weight in females. Candidate PODs, including the benchmark concentration lower confidence limits (BMCLs) from the selected models, are presented in Table 5.

<b>Table 5. Candidate PODs in Monkeys Administered Vinyl Bromide for the Derivation of the Subchronic p-RfC<sup>a</sup></b>	
<b>Endpoint</b>	<b>POD (HEC), mg/m<sup>3</sup></b>
Increased absolute liver weight (females) <sup>c</sup>	233.5 (LOAEL) <sup>d</sup>
Increased relative liver weight (females)	103.0 (BMCL <sub>10</sub> )
Decreased body weight (males)	233.5 (NOAEL) <sup>d</sup>

<sup>a</sup>[Leong and Torkelson \(1970\)](#); [Hazleton Laboratories \(1967\)](#).

<sup>b</sup>Modeling results are described in more detail in Appendix C.

<sup>c</sup>Chosen as the critical effect for deriving the subchronic p-RfC.

<sup>d</sup>BMD modeling did not provide adequate fit to the data.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration.

For decreased body weight in male monkeys, the data did not provide adequate model fit so the NOAEL (HEC) of 233.5 mg/m<sup>3</sup> is considered as a potential POD for this effect. BMD modeling was also not successful for increased absolute liver weight in female monkeys, so the LOAEL (HEC) of 233.5 mg/m<sup>3</sup> is identified as a potential POD. For increased relative liver weight in female monkeys, the BMCL<sub>10</sub> (HEC) of 103.0 mg/m<sup>3</sup> is considered as a potential POD. Of the potential PODs in monkeys exposed to vinyl bromide, the most sensitive is the BMCL<sub>10</sub> (HEC) of 103.0 mg/m<sup>3</sup> for increased relative liver weight in female monkeys. Although increased absolute liver weight in female monkeys occurred at the lowest tested concentration (233.5 mg/m<sup>3</sup>), the increase was only 10% which is the minimum change for this endpoint to be considered biologically significant. It is unlikely that a biologically significant change would be observed for increased absolute liver weight in female monkeys at 103.0 mg/m<sup>3</sup>, which is the BMCL<sub>10</sub> (HEC) for increased relative liver weight in female monkeys. Additionally, relative liver weight is a relatable index to absolute liver weight. In this case, it is likely that the BMCL<sub>10</sub> (HEC) for increased relative liver weight in female monkeys would also be protective for increased absolute liver weight. Also, the selection of the BMCL<sub>10</sub> (HEC) of 103.0 mg/m<sup>3</sup> for increased relative liver weight in female monkeys would be protective of decreased body weight in males (NOAEL [HEC] of 233.5 mg/m<sup>3</sup>). Therefore, the BMCL<sub>10</sub> (HEC) of 103.0 mg/m<sup>3</sup> for increased relative liver weight in female monkeys exposed to vinyl bromide vapors for up to 6 months (7 hours/day, 5 days/week), is selected as the point of departure (POD) for deriving the subchronic p-RfC. Increased liver weights were also observed in male and female rabbits that were exposed to vinyl bromide via inhalation for 6 months ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)). Furthermore, the study by [Benya et al. \(1982\)](#) identified the liver as the primary toxicity target of vinyl bromide in rats following inhalation exposure for longer than 6 months.

The subchronic p-RfC is derived by applying a composite uncertainty factor (UF<sub>C</sub>) of 300 (reflecting an interspecies uncertainty factor [UF<sub>A</sub>] of 3, an intraspecies uncertainty factor [UF<sub>H</sub>] of 10, and a database uncertainty factor [UF<sub>D</sub>] of 10) to the selected POD of 103.0 mg/m<sup>3</sup>.



$$\begin{aligned}
 \text{Subchronic p-RfC} &= \text{POD (HEC)} \div \text{UF}_C \\
 &= 103.0 \text{ mg/m}^3 \div 300 \\
 &= 3 \times 10^{-1} \text{ mg/m}^3
 \end{aligned}$$

Table 6 summarizes the uncertainty factors for the subchronic p-RfC for vinyl bromide.

<b>Table 6. Uncertainty Factors for the Subchronic p-RfC for Vinyl Bromide (CASRN 593-60-2)</b>		
<b>UF</b>	<b>Value</b>	<b>Justification</b>
UF <sub>A</sub>	3	A UF <sub>A</sub> of 3 (10 <sup>0.5</sup> ) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HEC calculation) is performed.
UF <sub>D</sub>	10	A UF <sub>D</sub> of 10 is applied to account for deficiencies and uncertainties in the database. The inhalation studies considered for derivation of the subchronic p-RfC for vinyl bromide are limited to two short-term studies in rats ( <a href="#">Leong and Torkelson, 1970</a> ; <a href="#">Dow Chemical, 1969</a> ; <a href="#">Hazleton Laboratories, 1967</a> ) and a 6-mo study in monkeys ( <a href="#">Leong and Torkelson, 1970</a> ; <a href="#">Hazleton Laboratories, 1967</a> ). Chronic inhalation data are limited to a 6-mo study in rats and rabbits and a single cancer bioassay in rats ( <a href="#">Benya et al., 1982</a> ). There are no reproductive or developmental toxicity studies available by inhalation, or oral exposure.
UF <sub>H</sub>	10	A UF <sub>H</sub> of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of vinyl bromide in humans.
UF <sub>L</sub>	1	A UF <sub>L</sub> of 1 is applied because the POD is a BMCL <sub>10</sub> .
UF <sub>S</sub>	1	A UF <sub>S</sub> of 1 is applied because the POD was derived from a 6-mo study, which is considered subchronic in monkeys.
UF <sub>C</sub>	300	Composite UF = UF <sub>A</sub> × UF <sub>D</sub> × UF <sub>H</sub> × UF <sub>L</sub> × UF <sub>S</sub> .

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; UF = uncertainty factor; UF<sub>A</sub> = interspecies uncertainty factor; UF<sub>D</sub> = database uncertainty factor; UF<sub>H</sub> = intraspecies uncertainty factor; UF<sub>L</sub> = LOAEL-to-NOAEL uncertainty factor; UF<sub>S</sub> = subchronic-to-chronic uncertainty factor.

Confidence in the subchronic p-RfC for vinyl bromide is low, as described in Table 7.

**Table 7. Confidence Descriptors for the Subchronic p-RfC for Vinyl Bromide (CASRN 593-60-2)**

Confidence Categories	Designation	Discussion
Confidence in study	L	Confidence in the principal study ( <a href="#">Leong and Torkelson, 1970</a> ; <a href="#">Hazleton Laboratories, 1967</a> ) is low. The study examined a variety of endpoints in monkeys, rats, and rabbits after 6 mo of exposure and in rats after 3 wk of exposure. However, only two exposure levels were tested, and the monkey and rabbit portions of the study utilized small sample sizes. The published paper included only limited description of results; much of the data were available only from the unpublished version ( <a href="#">Hazleton Laboratories, 1967</a> ) that was not peer-reviewed.
Confidence in database	L	Confidence in the database is low. The inhalation database for vinyl bromide includes a 4-wk study in rats ( <a href="#">Leong and Torkelson, 1970</a> ); a 6-mo study in monkeys, rats, and rabbits, with a 3-wk interim sacrifice in rats only ( <a href="#">Leong and Torkelson, 1970</a> ); and a 2-yr cancer bioassay in rats, with 6-, 12-, and 18-mo interim sacrifices ( <a href="#">Benya et al., 1982</a> ). Although published versions of all reports are available, they generally included only limited descriptions of the results. Much of the data were available only from the unpublished versions ( <a href="#">Huntingdon Research Center, 1979</a> ; <a href="#">Dorato, 1978</a> ; <a href="#">EPL, 1978</a> ; <a href="#">Dow Chemical, 1969</a> ; <a href="#">Hazleton Laboratories, 1967</a> ). There are no reproductive or developmental toxicity studies available by inhalation or oral exposure.
Confidence in subchronic p-RfC <sup>a</sup>	L	Overall confidence in the subchronic p-RfC is low.

<sup>a</sup>The overall confidence cannot be greater than the lowest entry in the table (low).

L = low; p-RfC = provisional reference concentration.

### Derivation of Chronic Provisional Reference Concentration

A chronic p-RfC value is not derived because an inhalation reference concentration (RfC) value is available on U.S. EPA's IRIS database ([U.S. EPA, 2003](#)). Table 8 summarizes the p-RfCs derived for vinyl bromide. Of note, the IRIS RfC was derived using the chronic inhalation study in rats from [Benya et al. \(1982\)](#).

**Table 8. Summary of Noncancer Reference Values for Vinyl Bromide (CASRN 593-60-2)**

Toxicity Type (units)	Species/ Sex	Critical Effect	p-Reference Value	POD Method	POD (HEC)	UF <sub>C</sub>	Principal Study
Subchronic p-RfD (mg/kg-d)	NDR						
Chronic p-RfD (mg/kg-d)	NDR						
Subchronic p-RfC (mg/m <sup>3</sup> )	Monkey/F	Increased relative liver weight	$3 \times 10^{-1}$	BMCL <sub>10</sub>	103.0	300	<a href="#">Leong and Torkelson (1970)</a> ; <a href="#">Hazleton Laboratories (1967)</a>
Chronic p-RfC (mg/m <sup>3</sup> )	RfC value of $3 \times 10^{-3}$ mg/m <sup>3</sup> is available on IRIS ( <a href="#">U.S. EPA, 2003</a> ). The value was derived using the chronic inhalation study in rats from <a href="#">Benya et al. (1982)</a> .						

BMCL = benchmark concentration lower confidence limit; F = female(s), HEC = human equivalent concentration; IRIS = Integrated Risk Information System; NDR = not determined; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfC = inhalation reference concentration; UF<sub>C</sub> = composite uncertainty factor.

## CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Following [U.S. EPA \(2005\)](#) *Guidelines for Carcinogen Risk Assessment*, vinyl bromide is “*Likely to Be Carcinogenic to Humans*” following inhalation exposure (see Table 9); there is “*Inadequate Information to Assess Carcinogenic Potential*” following oral exposure (see Table 9). No epidemiological studies or oral studies in animals are available to assess the carcinogenic potential of vinyl bromide. The “*Likely to Be Carcinogenic to Humans*” descriptor for vinyl bromide via the inhalation route is based on a single study in one species. Specifically, in a 2-year inhalation bioassay in rats, vinyl bromide was carcinogenic in both males and females ([Benya et al., 1982](#)). The most observed tumor type was angiosarcoma, primarily in the liver, with increased incidence in both sexes at all tested concentrations ( $\geq 42$  mg/m<sup>3</sup>). Increased incidence of hepatocellular carcinoma and neoplastic nodules (combined) was also observed in females at 42 mg/m<sup>3</sup>, and males and females at 1,080 mg/m<sup>3</sup>. Additionally, the incidence of Zymbal gland squamous cell carcinoma was significantly increased in males at  $\geq 1,080$  mg/m<sup>3</sup> and females at 5,402 mg/m<sup>3</sup>, and Zymbal gland papilloma incidence was significantly increased in males at 5,402 mg/m<sup>3</sup>. The available evidence from [Benya et al. \(1982\)](#) is consistent with one of the examples provided in the Cancer Guidelines ([U.S. EPA, 2005](#)) for the “*Likely to Be Carcinogenic to Humans*” descriptor. The example states that supporting data for this descriptor may include “an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans.” While the body of evidence is from a single study in a single species, the consistency of these findings to related compounds (vinyl chloride and vinyl fluoride) increases the confidence in the weight-of-evidence (WOE) descriptor ([NTP, 2016](#); [IARC, 2008](#)). Both vinyl chloride and vinyl fluoride induce hepatic angiosarcomas in laboratory animals via the same proposed mechanism as vinyl bromide (see “Mode-of-Action Discussion” below). Furthermore, epidemiological evidence indicates increased risk of hepatic angiosarcoma in humans exposed to vinyl chloride. The “*Likely to Be Carcinogenic to Humans*” descriptor for vinyl bromide via the inhalation route is further supported by the fact that both Zymbal gland tumors and angiosarcomas are considered rare tumors as discussed in the IRIS assessment for vinyl chloride ([U.S. EPA, 2000](#)). Another example for the “*Likely to Be Carcinogenic to Humans*” descriptor from the Cancer

Guidelines ([U.S. EPA, 2005](#)) is “a rare animal tumor response in a single experiment that is assumed to be relevant to humans.”

Table 9. Cancer WOE Descriptor for Vinyl Bromide			
Possible WOE Descriptor	Designation	Route of Entry (oral, inhalation, or both)	Comments
<i>“Carcinogenic to Humans”</i>	NS	NA	No adequate human data are available.
<i>“Likely to Be Carcinogenic to Humans”</i>	Selected	Inhalation	Vinyl bromide has been shown to produce angiosarcomas (predominantly in the liver), hepatocellular carcinomas and neoplastic nodules, and Zymbal gland tumors in male and female rats following inhalation exposure to concentrations $\geq 42$ mg/m <sup>3</sup> . Tumors were first observed between 6–12 mo of exposure. Additionally, angiosarcomas and Zymbal gland tumors are considered rare tumors. No adequate studies in other species were located.
<i>“Suggestive Evidence of Carcinogenic Potential”</i>	NS	NA	Evidence of the carcinogenic potential of vinyl bromide following inhalation exposure supports a stronger descriptor.
<i>“Inadequate Information to Assess Carcinogenic Potential”</i>	Selected	Oral	This descriptor is selected due to the lack of any information on the carcinogenicity of vinyl bromide by oral exposure.
<i>“Not Likely to Be Carcinogenic to Humans”</i>	NS	NA	The available data do not support this descriptor.

NA = not applicable; NS = not selected; WOE = weight of evidence.

## MODE-OF-ACTION 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.”

### Hypothesis

Tumors associated with vinyl bromide exposure in rats, including angiosarcoma, hepatocellular neoplasms, and Zymbal gland neoplasms, have a common genotoxic MOA ([NTP, 2016, 2015](#); [IARC, 2008](#); [ACGIH, 2001](#); [IARC, 1999](#)). Genotoxic events associated with vinyl bromide include direct-acting mutagenicity ([Ballerling et al., 1996](#); [Wagner et al., 1992](#); [Roldán-Arjona et al., 1991](#); [Lijinsky and Andrews, 1980](#); [Bartsch et al., 1979b](#)), formation of DNA

adducts ([Guengerich et al., 1981](#)), and formation of RNA adducts ([Laib et al., 1980](#); [Ottenwälder et al., 1979](#)). Studies using various metabolic inhibitors in hepatocytes indicate that 2-bromoethylene oxide is the primary DNA-binding agent, while 2-bromoacetaldehyde preferably binds protein because of its slower DNA-binding kinetics ([Guengerich, 1981](#); [Guengerich et al., 1981](#)). Based on analogy to vinyl chloride, the primary DNA adduct formed by 2-bromoethylene oxide is expected to be 7-(2-oxoethyl)guanosine; the minor adduct, N<sup>2</sup>,3-ethenoguanine, may also form ([Swenberg et al., 1992](#); [Bolt et al., 1981](#)). Additionally, based on further analogy to vinyl chloride as well as evidence following in vitro or in vivo exposure to vinyl bromide, cyclic ethenodeoxyadenosine and ethenodeoxycytidine RNA adducts would also readily form ([NTP, 2016, 2015](#); [Swenberg et al., 1992](#); [Bolt et al., 1981](#); [Laib et al., 1980](#); [Ottenwälder et al., 1979](#)). Both 2-bromoethylene oxide and 2-bromoacetaldehyde have been proposed to react with adenine and cytosine bases to form these etheno-RNA adducts ([NTP, 2016, 2015](#); [IARC, 2008, 1999](#); [Guengerich, 1981](#); [Barbin et al., 1975](#)). [Guengerich \(1981\)](#) proposed that 2-bromoacetaldehyde may have a greater contribution to DNA binding away from the site of metabolism (i.e., the hepatocyte), including reticuloendothelial cells associated with angiosarcomas.

Both DNA and RNA adducts expected following vinyl bromide exposure are considered promutagenic. The 7-(2-oxoethyl)guanosine DNA adduct is considered chemically unstable and can form potentially mutagenic abasic sites following spontaneous depurination, whereas the more stable mutagenic cyclic etheno adducts can result in DNA miscoding by modifying base-pairing sites ([Swenberg et al., 1992](#)). Because etheno adducts have a longer half-life than 7-(2-oxoethyl)guanosine adducts, they have a greater capacity for accumulation over time. Therefore, formation of promutagenic etheno adducts is considered the primary key event for tumor formation following exposure to vinyl halides (including vinyl bromide) ([NTP, 2016, 2015](#); [IARC, 2008, 1999](#); [Swenberg et al., 1992](#)).

#### ***Strength, Consistency, and Specificity of Association***

Available studies indicate that vinyl bromide can form etheno RNA adducts in vitro and in vivo ([Laib et al., 1980](#); [Ottenwälder et al., 1979](#)). Although the number of studies evaluating this proposed MOA for vinyl bromide is limited, this MOA is supported by similarities in reactive metabolites, adduct formation, and primary tumor type (hepatic angiosarcoma) to the established human carcinogen, vinyl chloride ([NTP, 2016, 2015](#); [IARC, 2008](#); [ACGIH, 2001](#); [IARC, 1999](#)).

#### ***Temporal and Dose-Response Concordance***

No studies have been identified that specifically evaluated both genotoxic events and tumor development. However, the available in vivo genotoxicity studies reported formation of promutagenic etheno adducts in the rat liver after a single 8-hour exposure to 250 ppm (1,090 mg/m<sup>3</sup>). In the 2-year cancer bioassay, tumors first appeared between 6 and 12 months of exposure to concentrations ≥1,080 mg/m<sup>3</sup> ([Huntingdon Research Center, 1979](#)). Therefore, etheno adduct formation is expected to occur prior to induction of tumors at relevant exposure levels.

#### ***Biological Plausibility and Coherence***

Formation of promutagenic, stable etheno RNA adducts is a proposed MOA for several compounds, including alkenes, vinyl halides, and other vinyl monomers ([Solomon, 1999](#)). Specifically, formation of etheno RNA adducts is a proposed common MOA for tumor formation

following exposure to vinyl chloride, vinyl bromide, and vinyl fluoride ([NTP, 2016](#)). All three vinyl halides cause angiosarcomas in animal bioassays and form similar DNA and RNA adducts. Additionally, human studies have found an association between vinyl chloride exposure and hepatic angiosarcomas ([NTP, 2016](#)). Therefore, this MOA is expected to be relevant to human exposure.

### **Mode-of-Action Conclusions**

Available evidence supports that formation of etheno DNA and RNA adducts by reactive metabolites can occur following exposure to vinyl bromide. This proposed MOA is plausible and consistent with proposed MOAs for related vinyl halides (vinyl chloride and vinyl fluoride). Based on human evidence for the related compound, vinyl chloride, the proposed MOA is relevant to human exposure.

## **DERIVATION OF PROVISIONAL CANCER RISK ESTIMATES**

### **Derivation of Provisional Oral Slope Factor**

Derivation of quantitative estimates of cancer risk following oral exposure to vinyl bromide is precluded by the absence of repeated-dose oral data for this compound.

### **Derivation of Provisional Inhalation Unit Risk**

One study in the inhalation database provided dose-response information for tumors induced by vinyl bromide ([Benya et al., 1982](#)). This study found significantly increased incidences of angiosarcomas, hepatocellular tumors, and Zymbal gland squamous cell carcinomas. These data are shown in Table B-13.

Benchmark dose (BMD) modeling was performed for each of these tumor types individually. Multistage cancer models in the U.S. EPA BMDS (Version 2.6) were fit to the incidence data for each tumor. The benchmark response (BMR) used was 10% extra risk. The HEC in mg/m<sup>3</sup> was used as the dose metric. The MS Combo model was used to evaluate the combined cancer risk of the multiple tumor types. MS Combo was run using the incidence data for the individual tumor types and the polydegrees identified in the model runs for the individual tumor types with adequate model fit. Modeling results are summarized in Table 10 (see additional BMD details in Appendix C).

<b>Table 10. Modeling Results Based on the Incidence of Tumors in S-D Rats Exposed to Vinyl Bromide via Inhalation for up to 24 Months<sup>a</sup></b>			
<b>Tumor Endpoint</b>	<b>Selected Model</b>	<b>BMC<sub>10</sub> (HEC) (mg/m<sup>3</sup>)</b>	<b>BMCL<sub>10</sub> (HEC) (mg/m<sup>3</sup>)</b>
<b>Males</b>			
Angiosarcoma	Multistage cancer (1-degree) <sup>b</sup>	12	9.6
Total hepatocellular neoplasms	Multistage cancer (1-degree) <sup>c</sup>	240	130
Zymbal gland squamous cell carcinoma	Multistage cancer (1-degree)	270	210
Combined male tumors	MS Combo <sup>d</sup>	11	9.0
<b>Females</b>			
Angiosarcoma	Multistage cancer (1-degree) <sup>b</sup>	8.4	6.8
Total hepatocellular neoplasms	No models provided adequate fit	NDr	NDr
Zymbal gland squamous cell carcinomas	Multistage cancer (1-degree)	1,000	620
Combined female tumors	MS Combo <sup>d</sup>	8.3	6.7

<sup>a</sup>[Benya et al. \(1982\)](#).

<sup>b</sup>Two highest concentrations dropped to achieve adequate fit.

<sup>c</sup>High concentration dropped to achieve adequate fit.

<sup>d</sup>Although angiosarcomas were observed in the liver, angiosarcomas are not specifically a liver tumor; therefore, it is appropriate to combine this tumor type with hepatocellular neoplasms.

BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., <sub>10</sub> = concentration associated with 10% extra risk); BMR = benchmark response; HEC = human equivalent concentration; NDr = not determined; S-D = Sprague-Dawley.

The Multistage cancer (1-degree) model provided an adequate fit to the data for angiosarcomas in males and females with the two highest concentrations dropped, total hepatocellular neoplasms in males with the high concentration dropped, and Zymbal gland squamous cell carcinomas in males females with the full data sets. Dropping of the high-concentration data was necessary for certain tumor types because lower incidences were observed at the highest concentration compared to the lower concentration groups, which the study authors attributed to high mortality. No models provided adequate fit to the data for total hepatocellular neoplasms (full data set or high concentration dropped) in females. Additional concentrations were not dropped due to lack of significance of findings at the next lowest concentration.

From the Multistage cancer models, the predicted benchmark concentrations associated with 10% extra risk (BMC<sub>10</sub>), and their 95% benchmark concentration lower confidence limits (BMCL<sub>10</sub>) for the individual tumor types ranged from 8.4 and 6.8 mg/m<sup>3</sup> (HEC), respectively, for angiosarcoma in females, to 270 and 210 mg/m<sup>3</sup> (HEC), respectively, for Zymbal gland squamous cell carcinoma in males. The combined tumor model for males resulted in BMC<sub>10</sub> and BMCL<sub>10</sub> estimates of 11 and 9.0 mg/m<sup>3</sup> (HEC), respectively. The combined tumor model (angiosarcomas and Zymbal gland squamous cell carcinomas) for females resulted in BMC<sub>10</sub> and BMCL<sub>10</sub> estimates of 8.3 and 6.7 mg/m<sup>3</sup> (HEC), respectively. The lowest BMCL<sub>10</sub> value of



6.7 mg/m<sup>3</sup> (HEC), based on the combined angiosarcomas and Zymbal gland squamous cell carcinomas in female rats was selected as the POD for deriving the provisional inhalation unit risk (p-IUR).

Evidence of a genotoxic MOA for vinyl bromide tumorigenesis indicates that the p-IUR for vinyl bromide should be derived using a linear approach. While there is evidence of saturable pharmacokinetics in rats following inhalation exposure to vinyl bromide ([Gargas and Andersen, 1982](#); [Andersen et al., 1980](#); [Filser and Bolt, 1979](#)), the two lowest exposure levels in the study by [Benya et al. \(1982\)](#) (42 and 230 mg/m<sup>3</sup>), and therefore the low-concentration extrapolation, are lower than exposure levels associated with saturation (≥240 mg/m<sup>3</sup>) ([Filser and Bolt, 1979](#)). Thus, based on mechanistic and toxicokinetic considerations, the p-IUR for vinyl bromide, based on the BMCL<sub>10</sub> (HEC) of 6.7 mg/m<sup>3</sup> for combined angiosarcomas and Zymbal gland squamous cell carcinomas in female rats exposed to vinyl bromide via inhalation for up to 24 months, was derived using a linear approach as follows:

$$\begin{aligned}\text{p-IUR} &= \text{BMR} \div \text{BMCL}_{10} \text{ (HEC)} \\ &= 0.1 \div 6.7 \text{ mg/m}^3 \\ &= 1.5 \times 10^{-2} \text{ (mg/m}^3\text{)}^{-1}\end{aligned}$$

Table 11 summarizes the cancer inhalation risk estimates derived.

<b>Table 11. Summary of Cancer Risk Estimates for Vinyl Bromide (CASRN 593-60-2)</b>				
<b>Toxicity Type (units)</b>	<b>Species/Sex</b>	<b>Tumor Type</b>	<b>Cancer Risk Estimate</b>	<b>Principal Study</b>
p-OSF (mg/kg-d) <sup>-1</sup>	NDr			
p-IUR (mg/m <sup>3</sup> ) <sup>-1</sup>	Rat/F	Combined angiosarcomas and Zymbal gland squamous cell carcinomas	1.5 × 10 <sup>-2</sup>	<a href="#">Benya et al. (1982)</a>

F = female(s); NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.



## **APPENDIX A. SCREENING PROVISIONAL VALUES**

For reasons noted in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) document, it is inappropriate to derive provisional reference doses (p-RfDs) or a provisional oral slope factor (p-OSF) for vinyl bromide. Available information for this chemical is also insufficient to support derivation of screening provisional toxicity values.

## APPENDIX B. DATA TABLES

<b>Table B-1. Body-Weight Data (in grams) for Male Wistar Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 4 Weeks (7 Hours/Day, 5 Days/Week)<sup>a</sup></b>		
<b>Exposure Duration (d)<sup>b, c</sup></b>	<b>Concentration Group, Analytical Concentration in mg/m<sup>3</sup> (HEC<sub>ER</sub>)</b>	
	<b>0</b>	<b>43,763 (9,117.3)</b>
0	281 ± 18	279 ± 20 (−0.7%)
2	290 ± 19	283 ± 21 (−2%)
5	305 ± 18	286 ± 21 (−6%)
10	316 ± 22	293 ± 21 (−7%)
15	342 ± 22	313 ± 18* (−9%)
20	353 ± 28	313 ± 19** (−11%)

<sup>a</sup>[Leong and Torkelson \(1970\)](#).

<sup>b</sup>Data are mean ± SEM; *n* = 10 controls, 5 exposed.

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.

\*Significantly different from control by Student's *t*-test (*p* < 0.05), as reported by the study authors.

\*\*Significantly different from control by Student's *t*-test (*p* < 0.01), as reported by the study authors.

HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; SEM = standard error of the mean.

Table B-2. Select Body- and Organ-Weight Data for Charles River Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 3 Weeks (7 Hours/Day, 5 Days/Week) <sup>a</sup>			
Endpoint <sup>b, c</sup>	Concentration Group, Analytical Concentration in mg/m <sup>3</sup> (HEC <sub>ER</sub> )		
	0	1,121 (233.5)	2,126 (442.9)
<b>Males</b>			
Body weight (g)	477 ± 46	482 ± 21 (+1%)	497 ± 38 (+4%)
Liver			
Absolute (g)	15.32 ± 2.08	14.43 ± 1.30 (−6%)	16.27 ± 2.54 (+6%)
Relative (% BW)	3.24 ± 0.70	2.99 ± 0.22 (−8%)	3.26 ± 0.32 (+0.6%)
Kidney			
Absolute (g)	3.25 ± 0.52	2.99 ± 0.17 (−8%)	2.86 ± 0.28 (−12%)
Relative (% BW)	0.573 ± 0.140	0.622 ± 0.055 (+9%)	0.576 ± 0.045 (+0.5%)
Heart			
Absolute (g)	1.26 ± 0.15	1.24 ± 0.10 (−2%)	1.19 ± 0.08 (−6%)
Relative (% BW)	0.266 ± 0.052	0.257 ± 0.026 (−3%)	0.242 ± 0.027 (−9%)
<b>Females</b>			
Body weight (g)	421 ± 83	349 ± 50 (−17%)	315 ± 22 (−25%)
Liver			
Absolute (g)	11.81 ± 0.58	13.09 ± 2.47 (+11%)	9.43 ± 2.24 (−20%)
Relative (% BW)	2.90 ± 0.64	3.74 ± 0.44 (+29%)	2.99 ± 0.63 (+3%)
Kidney			
Absolute (g)	2.09 ± 0.17	2.22 ± 0.32 (+6%)	1.71 ± 0.15* (−18%)
Relative (% BW)	0.411 ± 0.103	0.639 ± 0.091 (+56%)	0.542 ± 0.029 (+32%)
Heart			
Absolute (g)	1.03 ± 0.07	1.14 ± 0.28 (+11%)	0.97 ± 0.51 (−6%)
Relative (% BW)	0.252 ± 0.049	0.325 ± 0.066 (+29%)	0.31 ± 0.09 (+23%)
Ovary			
Absolute (g)	0.098 ± 0.022	0.132 ± 0.038 (−35%)	0.121 ± 0.029 (+24%)
Relative (% BW)	0.024 ± 0.005	0.073 ± 0.0082* (+204%)	0.0385 ± 0.0089* (+60%)

<sup>a</sup>Leong and Torkelson (1970); Hazleton Laboratories (1967).

<sup>b</sup>Data are mean ± SD; *n* = 5/group.

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.

\*Significantly different from control by ANOVA (*p* < 0.05), as reported by the study authors.

ANOVA = analysis of variance; BW = body weight; HEC<sub>ER</sub> = human equivalent concentration for extrapulmonary effects; SD = standard deviation.

Table B-3. Select Body- and Organ-Weight Data for Charles River Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6 Months (7 Hours/Day, 5 Days/Week) <sup>a</sup>			
Endpoint <sup>b, c</sup>	Concentration Group, Analytical Concentration in mg/m <sup>3</sup> (HEC <sub>ER</sub> )		
	0	1,121 (233.5)	2,126 (442.9)
<b>Males</b>			
Body weight (g)	606 ± 70	589 ± 61 (−3%)	581 ± 48 (−4%)
Liver			
Absolute (g)	17.80 ± 3.41	19.35 ± 3.36* (+9%)	17.79 ± 2.90 (−0.1%)
Relative (% BW)	2.93 ± 0.35	3.27 ± 0.35* (+12%)	3.05 ± 0.38 (+4%)
Kidney			
Absolute (g)	4.06 ± 0.50	3.95 ± 0.44 (−3%)	3.81 ± 0.47 (−6%)
Relative (% BW)	0.671 ± 0.063	0.672 ± 0.050 (+0.1%)	0.656 ± 0.073 (−2%)
Heart			
Absolute (g)	1.77 ± 0.24	1.96 ± 0.39 (+11%)	1.72 ± 0.22 (−3%)
Relative (% BW)	0.295 ± 0.042	0.332 ± 0.057* (+13%)	0.298 ± 0.038 (+1%)
<b>Females</b>			
Body weight (g)	372 ± 46	357 ± 39 (−4%)	347 ± 37 (−7%)
Liver			
Absolute (g)	12.26 ± 2.21	11.50 ± 1.88 (−6%)	11.89 ± 1.62 (−3%)
Relative (% BW)	3.29 ± 0.38	3.20 ± 0.25 (−3%)	3.43 ± 0.43 (+4%)
Kidney			
Absolute (g)	2.65 ± 0.31	2.56 ± 0.45 (−3%)	2.68 ± 0.33 (+1%)
Relative (% BW)	0.717 ± 0.089	0.720 ± 0.124 (+0.4%)	0.778 ± 0.126 (+9%)
Heart			
Absolute (g)	1.26 ± 0.26	1.39 ± 0.32 (+10%)	1.26 ± 0.15 (+0%)
Relative (% BW)	0.340 ± 0.071	0.396 ± 0.104* (+17%)	0.363 ± 0.054 (+7%)
Ovary			
Absolute (g)	0.134 ± 0.057	0.133 ± 0.033 (−0.7%)	0.113 ± 0.039 (−16%)
Relative (% BW)	0.0361 <sup>d</sup> ± 0.0161	0.0374 ± 0.0088 (+4%)	0.0326 ± 0.0116 (−10%)

<sup>a</sup>Leong and Torkelson (1970); Hazleton Laboratories (1967).

<sup>b</sup>Data are mean ± SD; *n* = 20–25/group.

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.

<sup>d</sup>Reported as 0.361 g; however, based on SD values, values reported in other groups, and lack of significant difference, it is assumed that this should be 0.0361 g.

\*Significantly different from control by ANOVA (*p* < 0.05), as reported by the study authors.

ANOVA = analysis of variance; BW = body weight; HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; SD = standard deviation.

Table B-4. Select Body- and Organ-Weight Data for Cynomolgus Monkeys Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6 Months (7 Hours/Day, 5 Days/Week) <sup>a</sup>			
Endpoint <sup>b, c</sup>	Concentration Group, Analytical Concentration in mg/m <sup>3</sup> (HEC <sub>ER</sub> )		
	0	1,121 (233.5)	2,126 (442.9)
<b>Males</b>			
Body weight (kg)	3.65 ± 0.354	3.59 ± 0.0173 (–2%)	2.75 ± 0.910 (–25%)
Liver			
Absolute (g)	63.4 ± 4.31	62.5 ± 2.27 (–1%)	50.2 ± 12.1 (–21%)
Relative (% BW)	1.75 ± 0.283	1.74 ± 0.0529 (–0.6)	1.88 ± 0.281 (+7%)
Kidney			
Absolute (g)	14.4 ± 0.424	12.6 ± 1.59 (–13%)	10.8 ± 1.82 (–25%)
Relative (% BW)	0.396 ± 0.0269	0.350 ± 0.0461 (–12%)	0.411 ± 0.0855 (+4%)
Spleen			
Absolute (g)	4.44 ± 1.94	6.05 ± 1.22 (+36%)	4.33 ± 1.10 (–3%)
Relative (% BW)	0.125 ± 0.065	0.169 ± 0.0340 (+35%)	0.175 ± 0.087 (+40%)
Thyroid			
Absolute (g)	0.405 ± 0.0778	0.427 ± 0.0895 (+5%)	0.257 ± 0.0666 (–37%)
Relative (% BW)	0.0112 ± 0.00320	0.0119 ± 0.00254 (+6%)	0.00973 ± 0.00222 (–13%)
<b>Females</b>			
Body weight (kg)	2.63 ± 0.512	2.30 ± 0.260 (–13%)	2.53 ± 0.911 (–4%)
Liver			
Absolute (g)	61.1 ± 7.31	67.5 ± 15.9 (+10%)	69.7 ± 29.5 (+14%)
Relative (% BW)	2.40 ± 0.574	2.91 ± 0.420 (+21%)	2.72 ± 0.402 (+13%)
Kidney			
Absolute (g)	12.1 ± 1.59	11.4 ± 2.38 (–6%)	11.9 ± 3.62 (–2%)
Relative (% BW)	0.465 ± 0.0326	0.497 ± 0.0816 (+7%)	0.477 ± 0.0360 (+3%)
Spleen			
Absolute (g)	4.91 ± 1.75	5.45 ± 1.73 (+11%)	6.51 ± 1.08 (+33%)
Relative (% BW)	0.193 ± 0.0700	0.234 ± 0.0542 (+21%)	0.268 ± 0.0480 (+39%)
Thyroid			
Absolute (g)	0.466 ± 0.153	0.303 ± 0.0431 (–35%)	0.295 ± 0.124 (–37%)
Relative (% BW)	0.0175 ± 0.00288	0.0132 ± 0.000757 (–25%)	0.0115 ± 0.000764 (–34%)

<sup>a</sup>Leong and Torkelson (1970); Hazleton Laboratories (1967).

<sup>b</sup>Data are mean ± SD; *n* = 2–4/group; means and SDs calculated for this review from individual animal data. The study authors stated that “statistical analyses showed that the differences were not significant.”

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean – control mean) ÷ control mean] × 100.

BW = body weight; HEC<sub>ER</sub> = human equivalent concentration for extraréspiratory effects; SD = standard deviation.

<b>Table B-5. Select Organ Weights for Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6 or 12 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup></b>					
<b>Endpoint<sup>b, c</sup></b>	<b>Concentration Group, Analytical Concentration in mg/m<sup>3</sup> (HEC<sub>ER</sub>)</b>				
	<b>0</b>	<b>42 (7.5)</b>	<b>230 (41)</b>	<b>1,080 (193)</b>	<b>5,402 (964.6)</b>
Body weight (g)					
6 mo	522 ± 19.8	488 ± 17.7 (-7%)	506 ± 17.7 (-3%)	545 ± 17.9 (+4%)	542 ± 51.3 (+4%)
12 mo	546 ± 28.3	575 ± 28.3 (+5%)	606 ± 19.0 (+11%)	592 ± 18.2 (+8%)	597 ± 23.0 (+9%)
Absolute liver weight (g)					
6 mo	11.5 ± 0.243	13.3 ± 0.872 (+16%)	13.6 ± 0.872** (+18%)	16.8 ± 1.10** (+46%)	13.6 ± 1.04 (+18%)
12 mo	12.9 ± 0.930	12.9 ± 0.785 (+0%)	15.3 ± 0.756 (+19%)	15.4 ± 0.853 (+20%)	16.3 ± 0.848** (+26%)
Relative liver weight (% BW)					
6 mo	2.21 ± 0.046	2.73 ± 0.115* (+24%)	2.68 ± 0.123* (+21%)	3.07 ± 0.127* (+39%)	2.54 ± 0.132 (+15%)
12 mo	2.33 ± 0.083	2.25 ± 0.106 (-3%)	2.52 ± 0.080 (+8%)	2.60 ± 0.120 (+12%)	2.71 ± 0.063* (+16%)
Absolute kidney weight (g)					
6 mo	2.8 ± 0.093	3.1 ± 0.22 (+11%)	2.8 ± 0.25 (+0%)	3.4 ± 0.18** (+21%)	3.2 ± 0.21 (+14%)
12 mo	3.0 ± 0.23	3.3 ± 0.17 (+10%)	3.8 ± 0.18** (+27%)	3.6 ± 0.37 (+20%)	3.6 ± 0.19** (+20%)
Relative kidney weight (% BW)					
6 mo	0.530 ± 0.0155	0.667 ± 0.0382* (+26%)	0.560 ± 0.037 (+6%)	0.626 ± 0.0147 * (+18%)	0.591 ± 0.0246 (+12%)
12 mo	0.56 ± 0.036	0.58 ± 0.025 (+4%)	0.62 ± 0.025 (+11%)	0.62 ± 0.075 (+11%)	0.59 ± 0.023 (+5%)
Absolute spleen weight (g)					
6 mo	0.4 ± 0.07	0.7 ± 0.2 (+75%)	0.4 ± 0.05 (+0%)	0.6 ± 0.08** (+50%)	0.8 ± 0.07** (+100%)
12 mo	0.53 ± 0.116	0.58 ± 0.074 (+9%)	1.0 ± 0.077** (+89%)	0.75 ± 0.131 (+42%)	0.83 ± 0.111 (+57%)
Relative spleen weight (% BW)					
6 mo	0.065 ± 0.0100	0.151 ± 0.0315* (+132%)	0.084 ± 0.0084 (+29%)	0.114 ± 0.0136 (+75%)	0.152 ± 0.0091* (+134%)
12 mo	0.097 ± 0.0202	0.103 ± 0.0129 (+6%)	0.166 ± 0.0138* (+71%)	0.129 ± 0.0243 (+33%)	0.143 ± 0.0223 (+47%)

<sup>a</sup>Benya et al. (1982); Huntingdon Research Center (1979).

<sup>b</sup>Data are mean ± SEM (variance data only reported for relative organ weights by the study authors; SEM calculated for body weight and absolute organ weights for this review);  $n = 4-10/\text{group}$ .

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean - control mean) ÷ control mean] × 100.

\*Significantly different from control by Mann-Whitney U test or Student's *t*-test ( $p < 0.05$ ), as reported by the study authors for relative organ weights (statistical analysis not reported by the study authors for body weight or absolute organ weights).

\*\*Significantly different from control by Student's *t*-test ( $p < 0.05$ ), as calculated for this review for body weight and absolute organ weights.

BW = body weight; HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; S-D = Sprague-Dawley; SEM = standard error of the mean.

<b>Table B-6. Select Organ Weights for Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6 or 12 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup></b>					
<b>Endpoint<sup>b, c</sup></b>	<b>Concentration Group, Analytical Concentration in mg/m<sup>3</sup> (HEC<sub>ER</sub>)</b>				
	<b>0</b>	<b>42 (7.5)</b>	<b>230 (41)</b>	<b>1,080 (193)</b>	<b>5,402 (964.6)</b>
Body weight (g)					
6 mo	293 ± 14.5	282 ± 17.9 (−4%)	308 ± 7.43 (+5%)	268 ± 6.38 (−9%)	270 ± 8.32 (−8%)
12 mo	360 ± 14.3	319 ± 10.7** (−11%)	348 ± 13.5 (−3%)	333 ± 8.43 (−8%)	333 ± 12.0 (−8%)
Absolute liver weight (g)					
6 mo	7.3 ± 0.48	7.8 ± 0.18 (+7%)	8.4 ± 0.17 (+15%)	7.2 ± 0.28 (−1%)	7.7 ± 0.45 (+6%)
12 mo	8.9 ± 0.50	8.3 ± 0.24 (−7%)	9.9 ± 0.51 (+11%)	9.0 ± 0.54 (+1%)	9.5 ± 0.92 (+6%)
Relative liver weight (% BW)					
6 mo	2.50 ± 0.107	2.83 ± 0.259 (+13%)	2.72 ± 0.083 (+9%)	2.68 ± 0.062 (+7%)	2.88 ± 0.195 (+15%)
12 mo	2.48 ± 0.083	2.61 ± 0.094 (+5%)	2.86 ± 0.118 (+15%)	2.71 ± 0.157 (+9%)	2.82 ± 0.207 (+14%)
Absolute kidney weight (g)					
6 mo	1.8 ± 0.21	2.3 ± 0.080 (+28%)	2.0 ± 0.068 (+11%)	1.6 ± 0.073 (−11%)	1.8 ± 0.024 (+0%)
12 mo	2.5 ± 0.19	2.1 ± 0.079** (−16%)	2.5 ± 0.18 (+0%)	1.9 ± 0.16** (−24%)	2.1 ± 0.14 (−16%)
Relative kidney weight (% BW)					
6 mo	0.61 ± 0.050	0.82 ± 0.066* (+34%)	0.66 ± 0.016 (+8%)	0.61 ± 0.034 (+0%)	0.69 ± 0.014 (+13%)
12 mo	0.71 ± 0.051	0.65 ± 0.032 (−9%)	0.70 ± 0.032 (−1%)	0.58 ± 0.045 (−18%)	0.63 ± 0.038 (−11%)
Absolute spleen weight (g)					
6 mo	0.4 ± 0.05	0.7 ± 0.08** (+75%)	0.6 ± 0.1 (+50%)	0.3 ± 0.02 (−25%)	0.5 ± 0.02 (+25%)
12 mo	0.6 ± 0.05	0.5 ± 0.03 (−17%)	0.6 ± 0.1 (+0%)	0.6 ± 0.08 (+0%)	1.2 ± 0.51 (+100%)
Relative spleen weight (% BW)					
6 mo	0.145 ± 0.0165	0.252 ± 0.0327* (+74%)	0.181 ± 0.0352 (+25%)	0.127 ± 0.0079 (−12%)	0.193 ± 0.0072* (+33%)
12 mo	0.1601 ± 0.01165	0.1618 ± 0.01142 (+1%)	0.1808 ± 0.02429 (+13%)	0.1648 ± 0.02148 (+3%)	0.3417 ± 0.1393 (+113%)

<sup>a</sup>Benya et al. (1982); Huntingdon Research Center (1979).

<sup>b</sup>Data are mean ± SEM (variance data only reported for relative organ weights by the study authors; SEM calculated for body weight and absolute organ weights for this review); *n* = 5–10/group.

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean − control mean) ÷ control mean] × 100.

\*Significantly different from control Mann-Whitney U test (*p* < 0.05), as reported by the study authors for relative organ weights (statistical analysis not reported by the study authors for body weight or absolute organ weights).

\*\*Significantly different from control by Student's *t*-test (*p* < 0.05), conducted for this review for body weight and absolute organ weights.

BW = body weight; HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; S-D = Sprague-Dawley; SEM = standard error of the mean.

<b>Table B-7. Hematological Data for Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6, 12, or 18 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup></b>					
<b>Endpoint<sup>b, c</sup></b>	<b>Concentration Group, Analytical Concentration in mg/m<sup>3</sup> (HEC<sub>ER</sub>)</b>				
	<b>0</b>	<b>42 (7.5)</b>	<b>230 (41)</b>	<b>1,080 (193)</b>	<b>5,402 (964.6)</b>
Hct (%)					
6 mo	41.0 ± 2.5	34.0 ± 2.1 (-17%)	42.0 ± 0.9 (+2%)	42.0 ± 0.7 (+2%)	43.0 ± 1.4 (+5%)
12 mo	37.0 ± 1.4	35.0 ± 1.0 (-5%)	39.0 ± 0.5 (+5%)	39.0 ± 0.7 (+5%)	34.0 ± 0.9 (-8%)
18 mo	38.0 ± 1.4	36.0 ± 2.0 (-5%)	37.0 ± 0.8 (-3%)	37.0 ± 1.2 (-3%)	32.0 ± 1.4* (-16%)
Hb (%)					
6 mo	14.00 ± 0.67	11.40 ± 0.76 (-19%)	14.50 ± 0.39 (+10%)	14.10 ± 0.12 (+0.7%)	14.20 ± 0.59 (+1%)
12 mo	12.80 ± 0.57	11.40 ± 0.28* (-11%)	13.20 ± 0.17 (+3%)	12.80 ± 0.28 (+0%)	11.00 ± 0.28* (-14%)
18 mo	11.80 ± 0.49	11.40 ± 0.69 (-3%)	12.30 ± 0.29 (+4%)	12.10 ± 0.35 (+3%)	10.70 ± 0.51 (-9%)
RBC count (10 <sup>6</sup> /mm <sup>3</sup> )					
6 mo	7.32 ± 0.40	5.86 ± 0.32 (-20%)	7.38 ± 0.08 (+0.8%)	7.49 ± 0.21 (+2%)	7.56 ± 0.22 (+3%)
12 mo	6.56 ± 0.29	6.40 ± 0.20 (-2%)	6.90 ± 0.14 (+5%)	6.16 ± 0.15 (-6%)	5.70 ± 0.23* (-13%)
18 mo	6.46 ± 0.27	6.17 ± 0.37 (-5%)	6.65 ± 0.15 (+3%)	6.94 ± 0.22 (+7%)	5.91 ± 0.26 (-9%)
MCV (μm <sup>3</sup> )					
6 mo	55.37 ± 0.50	57.32 ± 0.97 (+4%)	56.19 ± 0.91 (+2%)	56.19 ± 1.29 (+2%)	56.90 ± 0.70 (+3%)
12 mo	56.80 ± 0.91	54.80 ± 0.74 (-4%)	56.20 ± 0.45 (-1%)	62.80 ± 1.28* (+11%)	60.10 ± 1.26* (+6%)
18 mo	58.50 ± 0.82	58.70 ± 1.19 (+0.3%)	56.30 ± 0.55 (-4%)	53.90 ± 0.46* (-8%)	54.90 ± 0.64* (-6%)
WBC count (10 <sup>3</sup> /mm <sup>3</sup> )					
6 mo	4.70 ± 0.42	7.50 ± 1.47 (+60%)	4.50 ± 0.70 (-4%)	4.60 ± 0.45 (-2%)	7.10 ± 0.84 (+51%)
12 mo	4.90 ± 0.71	4.60 ± 0.61 (-6%)	4.70 ± 0.66 (-4%)	7.60 ± 2.07 (+55%)	7.80 ± 0.84* (+59%)
18 mo	6.90 ± 0.71	7.00 ± 1.85 (+1%)	6.80 ± 0.56 (-1%)	8.70 ± 2.33 (+26%)	11.50 ± 2.02 (+67%)

<sup>a</sup>Benya et al. (1982).

<sup>b</sup>Data are mean ± SEM; *n* = 5–10/group.

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean – control mean) ÷ control mean] × 100.

\*Significantly different from control by Mann-Whitney U test or Student's *t*-test (*p* < 0.05), as reported by the study authors.

Hb = hemoglobin; Hct = hematocrit; HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; MCV = mean corpuscular volume; RBC = red blood cell; S-D = Sprague-Dawley; SEM = standard error of the mean; WBC = white blood cell.



<b>Table B-8. Hematological Data for Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6, 12, or 18 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup></b>					
<b>Endpoint<sup>b, c</sup></b>	<b>Concentration Group, Analytical Concentration in mg/m<sup>3</sup> (HEC<sub>ER</sub>)</b>				
	<b>0</b>	<b>42 (7.5)</b>	<b>230 (41)</b>	<b>1,080 (193)</b>	<b>5,402 (964.6)</b>
Hct (%)					
6 mo	37.0 ± 0.7	40.0 ± 0.5 (+8%)	39.0 ± 0.7 (+5%)	38.0 ± 1.5 (+3%)	41.0 ± 1.5 (+11%)
12 mo	39.0 ± 0.8	39.0 ± 0.9 (+0%)	36.0 ± 1.3 (-8%)	36.0 ± 1.3 (-8%)	35.0 ± 1.7 (-10%)
18 mo	41.0 ± 0.8	37.0 ± 3.2 (-10%)	36.0 ± 1.7 (-12%)	36.0 ± 1.8* (-12%)	27.0 ± 1.7* (-34%)
Hb (%)					
6 mo	13.10 ± 0.26	13.80 ± 0.25 (+5%)	13.90 ± 0.14 (+6%)	13.60 ± 0.46 (+4%)	13.90 ± 0.39 (+6%)
12 mo	13.30 ± 0.31	12.70 ± 0.28 (-5%)	12.30 ± 0.51 (-8%)	12.30 ± 0.56 (-8%)	11.50 ± 0.65* (-14%)
18 mo	12.80 ± 0.18	11.90 ± 1.12 (-7%)	11.80 ± 0.06 (-8%)	12.10 ± 0.54 (-6%)	9.30 ± 0.58* (-27%)
RBC count (10 <sup>6</sup> /mm <sup>3</sup> )					
6 mo	6.74 ± 0.12	6.77 ± 0.13 (+0.4%)	6.32 ± 0.13 (-6%)	6.63 ± 0.20 (-2%)	6.94 ± 0.23 (+3%)
12 mo	6.41 ± 0.17	6.71 ± 0.21 (+5%)	6.00 ± 0.27 (-6%)	5.87 ± 0.28 (-8%)	5.60 ± 0.32 (-13%)
18 mo	6.38 ± 0.12	6.02 ± 0.57 (-6%)	5.84 ± 0.32 (-9%)	6.09 ± 0.31 (-5%)	4.77 ± 0.36* (-25%)
MCV (μm <sup>3</sup> )					
6 mo	55.21 ± 0.40	58.49 ± 0.64 (+6%)	61.11 ± 0.41 (+11%)	56.64 ± 0.79 (+3%)	58.54 ± 1.58* (+6%)
12 mo	60.50 ± 0.97	58.00 ± 1.41 (-4%)	60.30 ± 0.97 (-0.3%)	62.00 ± 1.25 (+3%)	62.60 ± 1.66 (+4%)
18 mo	64.10 ± 1.39	62.40 ± 2.19 (-3%)	62.80 ± 1.73 (-2%)	59.90 ± 0.89* (-7%)	57.60 ± 3.33* (-10%)
WBC count (10 <sup>3</sup> /mm <sup>3</sup> )					
6 mo	1.90 ± 0.18	3.10 ± 0.18* (+63%)	3.20 ± 0.50 (+68%)	5.20 ± 2.00 (+174%)	4.10 ± 0.30* (+116%)
12 mo	2.30 ± 0.27	2.30 ± 0.22 (+0%)	2.00 ± 0.34 (-13%)	3.40 ± 1.43 (+48%)	14.50 ± 8.01 (+530%)
18 mo	3.80 ± 0.28	5.60 ± 2.28 (+47%)	5.20 ± 0.86 (+37%)	4.80 ± 0.70 (+26%)	4.00 ± 1.41 (+5%)

<sup>a</sup>Benya et al. (1982).

<sup>b</sup>Data are mean ± SEM; *n* = 5–10/group.

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean – control mean) ÷ control mean] × 100.

\*Significantly different from control by Mann-Whitney U test or Student's *t*-test (*p* < 0.05), as reported by the study authors.

Hb = hemoglobin; Hct = hematocrit; HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; MCV = mean corpuscular volume; RBC = red blood cell; S-D = Sprague-Dawley; SEM = standard error of the mean; WBC = white blood cell.

**Table B-9. Serum Chemistry Data for Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6, 12, or 18 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup>**

Endpoint <sup>b, c</sup>	Concentration Group, Analytical Concentration in mg/m <sup>3</sup> (HEC <sub>ER</sub> )				
	0	42 (7.5)	230 (41)	1,080 (193)	5,402 (964.6)
BUN (mU/mL)					
6 mo	18.0 ± 1.3	2.70 ± 1.8* (-85%)	17.0 ± 0.7 (-6%)	16.0 ± 1.0 (-11%)	18.0 ± 1.5 (+0%)
12 mo	24.0 ± 1.2	27.0 ± 1.4 (+13%)	31.0 ± 1.1* (+29%)	32.0 ± 2.8* (+33%)	28.0 ± 3.2 (+17%)
18 mo	20.0 ± 1.1	22.0 ± 2.2 (+10%)	19.0 ± 0.8 (-5%)	19.0 ± 0.9 (-5%)	15.0 ± 0.8* (-25%)
ALP (mU/mL)					
6 mo	189.0 ± 9.2	182.0 ± 39.8 (-4%)	234.0 ± 11.9* (+24%)	192.0 ± 18.0 (+2%)	286.0 ± 39.8 (+51%)
12 mo	194.0 ± 11.8	233.0 ± 19.9 (+20%)	195.0 ± 10.4 (+0.5%)	233.0 ± 39.6 (+20%)	290.0 ± 73.9 (+50%)
18 mo	185.0 ± 14.7	261.0 ± 56.1 (+41%)	166.0 ± 14.8 (-10%)	280.0 ± 60.6 (+51%)	266.0 ± 33.1* (+44%)
AST (mU/mL)					
6 mo	109.0 ± 14.4	378.0 ± 161.9* (+247%)	89.0 ± 7.4 (-18%)	113.0 ± 21.5 (+4%)	111.0 ± 11.8 (+2%)
12 mo	144.0 ± 15.8	116.0 ± 12.4 (-19%)	108.0 ± 16.2 (-25%)	119.0 ± 12.7 (-17%)	138.0 ± 12.5 (-4%)
18 mo	96.0 ± 7.8	129.0 ± 17.7 (+34%)	89.0 ± 9.3 (-7%)	144.0 ± 12.6* (+50%)	172.0 ± 55.6 (+79%)
LDH (mU/mL)					
6 mo	318.0 ± 38.2	1,600.0 ± 1134 (+403%)	331.0 ± 49.7 (+4%)	338.0 ± 128.2 (+6%)	1,127.0 ± 274.9* (+254%)
12 mo	434.0 ± 142.3	483.0 ± 87.2 (+11%)	447.0 ± 103.9 (+3%)	320.0 ± 98.3 (-26%)	784.0 ± 93.3 (+81%)
18 mo	746.0 ± 183.0	921.0 ± 162.8 (+24%)	347.0 ± 78.2 (-54%)	1,360.0 ± 231.0 (+82%)	384.0 ± 73.1 (-49%)

<sup>a</sup>Benya et al. (1982).

<sup>b</sup>Data are mean ± SEM; *n* = 5–10/group.

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean – control mean) ÷ control mean] × 100.

\*Significantly different from control by Student's *t*-test (*p* < 0.05), as reported by the study authors.

ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; LDH = lactate dehydrogenase; S-D = Sprague-Dawley; SEM = standard error of the mean.

**Table B-10. Serum Chemistry Data for Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6, 12, or 18 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup>**

Endpoint <sup>b, c</sup>	Concentration Group, Analytical Concentration in mg/m <sup>3</sup> (HEC <sub>ER</sub> )				
	0	42 (7.5)	230 (41)	1,080 (193)	5,402 (964.6)
BUN (mU/mL)					
6 mo	18.0 ± 0.2	18.0 ± 1.3 (+0%)	18.0 ± 1.1 (+0%)	16.0 ± 1.5 (-11%)	18.0 ± 1.2 (+0%)
12 mo	26.0 ± 1.3	25.0 ± 1.0 (-4%)	32.0 ± 2.4 (+23%)	33.0 ± 1.9* (+27%)	28.0 ± 2.4 (+8%)
18 mo	20.0 ± 2.0	22.0 ± 3.3 (+10%)	20.0 ± 2.6 (+0%)	23.0 ± 2.0 (+15%)	16.0 ± 0.7* (-20%)
ALP (mU/mL)					
6 mo	140.0 ± 16.4	118.0 ± 9.1 (-16%)	152.0 ± 20.3 (+9%)	140.0 ± 12.9 (+0%)	128.0 ± 9.1 (-9%)
12 mo	124.0 ± 6.3	98.0 ± 7.7* (-21%)	119.0 ± 11.4 (-4%)	185.0 ± 43.7 (+49%)	208.0 ± 56.1* (+68%)
18 mo	157.0 ± 20.9	168.0 ± 30.1 (+7%)	151.0 ± 20.9 (-4%)	165.0 ± 15.5 (+5%)	137.0 ± 12.5 (-13%)
AST (mU/mL)					
6 mo	123.0 ± 10.2	87.0 ± 8.2 (-29%)	88.0 ± 7.0* (-29%)	97.0 ± 12.4 (-21%)	83.0 ± 0.6* (-33%)
12 mo	93.0 ± 10.9	91.0 ± 9.7 (-2%)	116.0 ± 17.1 (+25%)	104.0 ± 11.7 (+12%)	121.0 ± 23.9 (+30%)
18 mo	82.0 ± 5.3	124.0 ± 23.4 (+51%)	92.0 ± 13.3 (+12%)	123.0 ± 19.0 (+50%)	115.0 ± 23.5 (+40%)
LDH (mU/mL)					
6 mo	174.0 ± 41.1	216.0 ± 77.6 (+24%)	187.0 ± 35.8 (+8%)	531.0 ± 133.3* (+205%)	515.0 ± 91.0* (+196%)
12 mo	234.0 ± 34.7	296.0 ± 53.8 (+27%)	349.0 ± 64.7 (+49%)	247.0 ± 71.2 (+6%)	640.0 ± 114.7* (+174%)
18 mo	188.0 ± 24.1	723.0 ± 238.3* (+285%)	227.0 ± 358 (+21%)	868.0 ± 190.9* (+362%)	604.0 ± 179.3 (+221%)

<sup>a</sup>Benya et al. (1982).

<sup>b</sup>Data are mean ± SEM; *n* = 5–10/group.

<sup>c</sup>Value in parentheses is % change relative to control = [(treatment mean – control mean) ÷ control mean] × 100.

\*Significantly different from control by Student's *t*-test (*p* < 0.05), as reported by the study authors.

ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; LDH = lactate dehydrogenase; S-D = Sprague-Dawley; SEM = standard error of the mean.

<b>Table B-11. Non-neoplastic Liver Lesions in Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup></b>					
<b>Endpoint<sup>b</sup></b>	<b>Concentration Group, Analytical Concentration in mg/m<sup>3</sup> (HEC<sub>ER</sub>)</b>				
	<b>0</b>	<b>42 (7.5)</b>	<b>230 (41)</b>	<b>1,080 (193)</b>	<b>5,402 (964.6)</b>
Eosinophilic foci					
12-mo interim sacrifice	0/10 (0%)	NE	1/10 (10%)	0/10 (0%)	1/10 (10%)
18-mo interim sacrifice	1/10 (10%)	2/10 (20%)	8/10* (80%)	6/10 (60%)	3/10 (30%)
18-mo terminal sacrifice <sup>c</sup>	NA	NA	NA	NA	1/19 (5%)
24-mo terminal sacrifice	14/74 (19%)	22/52* (42%)	11/28* (39%)	1/6 (17%)	NA
Basophilic foci					
12-mo interim sacrifice	1/10 (10%)	NE	1/10 (10%)	0/10 (0%)	1/10 (10%)
18-mo interim sacrifice	0/10 (0%)	1/10 (10%)	5/10* (50%)	6/10* (60%)	6/10* (60%)
18-mo terminal sacrifice <sup>c</sup>	NA	NA	NA	NA	5/19** (26%)
24-mo terminal sacrifice	9/74 (12%)	16/52* (31%)	11/28* (39%)	0/6 (0%)	NA
Focal hepatocyte hypertrophy					
12-mo interim sacrifice	0/10 (0%)	NE	0/10 (0%)	0/10 (0%)	0/10 (0%)
18-mo interim sacrifice	0/10 (0%)	4/10 (40%)	8/10* (80%)	9/10* (90%)	10/10* (100%)
18-mo terminal sacrifice <sup>c</sup>	NA	NA	NA	NA	NR
24-mo terminal sacrifice	NR	NR	NR	NR	NA
Peliosis					
12-mo interim sacrifice	0/10 (0%)	NE	0/10 (0%)	0/10 (0%)	0/10 (0%)
18-mo interim sacrifice	0/10 (0%)	3/10 (30%)	5/10* (50%)	6/10* (60%)	4/10 (40%)
18-mo terminal sacrifice <sup>c</sup>	NA	NA	NA	NA	NR
24-mo terminal sacrifice	NR	NR	NR	NR	NA

<sup>a</sup>Benya et al. (1982); Ethyl Corporation (1979); Huntingdon Research Center (1979); EPL (1978).

<sup>b</sup>Values denote number of animals showing changes ÷ total number of animals examined (% incidence).

<sup>c</sup>All surviving rats in 5,402-mg/m<sup>3</sup> group were sacrificed at 18 months due to high group mortality (>50%).

\*Significantly increased compared with control by Fisher's exact test ( $p < 0.05$ ), conducted for this review.

\*\*Combined 18-month interim and terminal data are significantly different from interim 18-month control data by Fisher's exact test ( $p < 0.05$ ), conducted for this review.

HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; NA = not applicable; NE = not examined; NR = not reported; S-D = Sprague-Dawley.

**Table B-12. Non-neoplastic Liver Lesions in Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup>**

Endpoint <sup>b</sup>	Concentration Group, Analytical Concentration in mg/m <sup>3</sup> (HEC <sub>ER</sub> )				
	0	42 (7.5)	230 (41)	1,080 (193)	5,402 (964.6)
Eosinophilic foci					
12-mo interim sacrifice	0/10 (0%)	NE	1/10 (10%)	1/10 (10%)	0/10 (0%)
18-mo interim sacrifice	1/10 (10%)	1/10 (10%)	2/10 (20%)	4/10 (40%)	0/10 (0%)
18-mo terminal sacrifice <sup>c</sup>	NA	NA	NA	NA	1/43 (2%)
24-mo terminal sacrifice	3/47 (6%)	4/48 (8%)	2/67 (3%)	2/83 (2%)	NA
Basophilic foci					
12-mo interim sacrifice	0/10 (0%)	NE	0/10 (0%)	2/10 (20%)	2/10 (20%)
18-mo interim sacrifice	0/10 (0%)	2/10 (20%)	4/10 (40%)	4/10 (40%)	3/10 (30%)
18-mo terminal sacrifice <sup>c</sup>	NA	NA	NA	NA	0/43 (0%)
24-mo terminal sacrifice	2/47 (4%)	10/48* (21%)	7/67 (10%)	5/83 (6%)	NA
Focal hepatocyte hypertrophy					
12-mo interim sacrifice	0/10 (0%)	NE	0/10 (0%)	0/10 (0%)	0/10 (0%)
18-mo interim sacrifice	0/10 (0%)	3/10 (30%)	5/10* (50%)	8/10* (80%)	6/10* (60%)
18-mo terminal sacrifice <sup>c</sup>	NA	NA	NA	NA	NR
24-mo terminal sacrifice	NR	NR	NR	NR	NA
Peliosis					
12-mo interim sacrifice	0/10 (0%)	NE	0/10 (0%)	0/10 (0%)	0/10 (0%)
18-mo interim sacrifice	0/10 (0%)	5/10* (50%)	4/10 (40%)	3/10 (30%)	0/10 (0%)
18-mo terminal sacrifice <sup>c</sup>	NA	NA	NA	NA	NR
24-mo terminal sacrifice	NR	NR	NR	NR	NA

<sup>a</sup>[Benya et al. \(1982\)](#); [Ethyl Corporation \(1979\)](#); [Huntingdon Research Center \(1979\)](#); [EPL \(1978\)](#).

<sup>b</sup>Values denote number of animals showing changes ÷ total number of animals examined (% incidence).

<sup>c</sup>All surviving rats in 5,402-mg/m<sup>3</sup> group were sacrificed at 18 months due to high mortality (>50%).

\*Significantly increased compared with control by Fisher's exact test ( $p < 0.05$ ), conducted for this review.

HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; NA = not applicable; NE = not examined; NR = not reported; S-D = Sprague-Dawley.

<b>Table B-13. Select Neoplastic Lesions in S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months (6 Hours/Day, 5 Days/Week)<sup>a</sup></b>					
<b>Endpoint<sup>b</sup></b>	<b>Concentration Group, Analytical Concentration in mg/m<sup>3</sup> (HEC<sub>ER</sub>)</b>				
	<b>0</b>	<b>42 (7.5)</b>	<b>230 (41)</b>	<b>1,080 (193)</b>	<b>5,402 (964.6)<sup>c</sup></b>
<b>Males</b>					
Angiosarcoma <sup>d</sup>	0/144 (0%)	7/120* (6%)	36/120* (30%)	61/120* (51%)	43/120* (36%)
Hepatocellular carcinoma	3/143 (2%)	1/103 (1%)	7/119 (6%)	9/120 (8%)	3/119 (3%)
Hepatic neoplastic nodules	1/143 (0.7%)	4/103 (4%)	3/119 (3%)	4/120 (3%)	2/119 (2%)
Total hepatocellular neoplasms	4/143 (3%)	5/103 (5%)	10/119 (8%)	13/120* (11%)	5/119 (4%)
Zymbal gland squamous cell carcinoma	2/142 (1%)	1/99 (1%)	1/112 (0.9%)	13/114* (11%)	35/116* (30%)
Zymbal gland papilloma	0/142 (0%)	0/99 (0%)	1/112 (0.9%)	3/114 (3%)	5/116* (4%)
<b>Females</b>					
Angiosarcoma <sup>d</sup>	1/144 (0.7%)	10/120* (8%)	50/120* (42%)	61/120* (51%)	41/120* (34%)
Hepatocellular carcinoma	4/142 (3%)	6/101 (6%)	3/113 (3%)	11/118 (9%)	4/112 (4%)
Hepatic neoplastic nodules	3/142 (2%)	12/101 (12%)	9/113 (8%)	10/118 (8%)	5/112 (4%)
Total hepatocellular neoplasms	7/142 (5%)	18/101* (18%)	12/113 (11%)	21/118* (18%)	9/112 (8%)
Zymbal gland squamous cell carcinoma	0/139 (0%)	0/99 (0%)	3/113 (3%)	2/119 (2%)	11/114* (10%)
Zymbal gland papilloma	0/139 (0%)	0/99 (0%)	0/113 (0%)	0/119 (0%)	3/114 (3%)

<sup>a</sup>[Benya et al. \(1982\)](#).

<sup>b</sup>Values denote number of animals showing changes ÷ total number of animals examined (% incidence); the denominator includes terminal sacrifice, interim sacrifices, and all animals found dead or sacrificed moribund.

<sup>c</sup>All surviving rats in this group sacrificed at 18 months due to high mortality (>50%).

<sup>d</sup>The majority of angiosarcomas were observed in the liver; occasional incidences were observed in lung, spleen, nasal cavity, and mesentery.

\*Significantly different from control by Yates-corrected  $\chi^2$  test ( $p < 0.05$ ), as reported by the study authors.

HEC<sub>ER</sub> = human equivalent concentration for extrarespiratory effects; S-D = Sprague-Dawley.

## APPENDIX C. BENCHMARK DOSE MODELING RESULTS

### MODELING PROCEDURE FOR CONTINUOUS NONCANCER DATA

Benchmark dose (BMD) modeling of continuous data is conducted with U.S. EPA's Benchmark Dose Software (BMDS, Version 2.7). All continuous models available within the software are fit using a benchmark response (BMR) of 1 standard deviation (SD) relative risk or 10% extra risk when a biologically determined BMR is available (e.g., BMR 10% relative deviation [RD] for body weight based on a biologically significant weight loss of 10%), as outlined in the *Benchmark Dose Technical Guidance* ([U.S. EPA, 2012b](#)). An adequate fit is judged based on the  $\chi^2$  goodness-of-fit  $p$ -value ( $p > 0.1$ ), magnitude of the scaled residuals near the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination is made as to whether the variance across dose groups is homogeneous. If a homogeneous variance model is deemed appropriate based on the statistical test provided by BMDS (i.e., Test 2), the final BMD results are estimated from a homogeneous variance model. If the test for homogeneity of variance is rejected ( $p < 0.1$ ), the model is run again while modeling the variance as a power function of the mean to account for this nonhomogeneous variance. If this nonhomogeneous variance model does not adequately fit the data (i.e., Test 3;  $p < 0.1$ ), the data set is considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest benchmark dose lower confidence limit/benchmark concentration lower confidence limit (BMDL/BMCL) is selected if the BMDL/BMCL estimates from different models vary >threefold; otherwise, the BMDL/BMCL from the model with the lowest Akaike's information criterion (AIC) is selected as a potential POD from which to derive the oral reference dose/inhalation reference concentration (RfD/RfC).

### BMD MODELING TO IDENTIFY POTENTIAL POINTS OF DEPARTURE FOR THE DERIVATION OF A SUBCHRONIC PROVISIONAL REFERENCE CONCENTRATION

As discussed in the body of the report under "Derivation of Subchronic Provisional Reference Concentration," the most sensitive treatment-related changes due to inhalation exposure of vinyl bromide were reported in male and female monkeys from the ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)) study and are presented in Table B-4. Endpoints selected to determine potential PODs for the subchronic provisional reference concentration (p-RfC) using BMD analysis were as follows: (1) decreased body weight in male monkeys, (2) increased absolute liver weight in female monkeys, and (3) increased relative liver weight in female monkeys.

#### Model Predictions for Decreased Body Weight in Male Monkeys Treated with Vinyl Bromide via Inhalation for 6 Months

The procedure outlined above for continuous data was applied to the data for decreased body weight in male monkeys treated with vinyl bromide via inhalation for 6 months ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)). Table C-1 summarizes the BMD modeling results. Neither the constant nor the nonconstant variance models provided adequate fit to the variance data; thus, these data were not suitable for BMD modeling.

**Table C-1. Modeling Results for Decreased Body Weight in Male Monkeys Administered Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6 Months<sup>a\*</sup>**

Model	Test for Significant Difference <i>p</i> -Value <sup>b</sup>	Variance <i>p</i> -Value <sup>c</sup>	Means <i>p</i> -Value <sup>c</sup>	Scaled Residuals for Dose Group <sup>d</sup>	AIC	BMC <sub>10</sub> (mg/m <sup>3</sup> )	BMCL <sub>10</sub> (mg/m <sup>3</sup> )
<b>Nonconstant variance</b>							
Exponential (Model 2) <sup>e</sup>	<0.0001	0.1118	<0.0001	0.9085	2.056236	285.973	124.009
Exponential (Model 3) <sup>e</sup>	<0.0001	0.1118	NDr	$1.25 \times 10^{-5}$	-2.021505	420.064	274.274
Exponential (Model 4) <sup>e</sup>	<0.0001	0.1118	<0.0001	0.9085	2.056236	285.973	107.147
Exponential (Model 5) <sup>e</sup>	<0.0001	NDr	NDr	NDr	NDr	NDr	NDr
Hill <sup>e</sup>	<0.0001	NDr	NDr	NDr	NDr	NDr	NDr
Linear <sup>f</sup>	<0.0001	0.1118	<0.0001	0.937	1.845925	276.649	133.891
Polynomial (2-degree) <sup>f</sup>	<0.0001	0.1118	0.0002728	0.666	-1.10378	306.487	224.891
Polynomial (3-degree) <sup>f</sup>	<0.0001	0.1118	0.0006902	0.311	-2.836675	331.014	270.064
Power <sup>e</sup>	<0.0001	0.1118	0.001308	$1.30 \times 10^{-5}$	-4.021509	421.965	276.516

<sup>a</sup>[Leong and Torkelson \(1970\)](#); [Hazleton Laboratories \(1967\)](#).

<sup>b</sup>Values >0.05 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Values <0.10 fail to meet conventional goodness-of-fit criteria.

<sup>d</sup>Scaled residuals at concentrations closest to BMC.

<sup>e</sup>Power restricted to  $\geq 1$ .

<sup>f</sup>Coefficients restricted to be negative.

\*No model was selected. Neither the constant nor nonconstant variance models provide adequate fit to the variance data.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMC<sub>10</sub> = benchmark concentration 10% extra risk; BMCL<sub>10</sub> = 95% benchmark concentration lower confidence limit; NDr = not determined.



**Model Predictions for Increased Absolute Liver Weight in Female Monkeys Treated with Vinyl Bromide via Inhalation for 6 Months**

The procedure outlined above for continuous data was applied to the data for increased absolute liver weight in female monkeys treated with vinyl bromide via inhalation for 6 months ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)). Table C-2 summarizes the BMD modeling results. Neither the constant nor the nonconstant variance models provided adequate fit to the variance data; thus, these data were not suitable for BMD modeling.

**Table C-2. Modeling Results for Increased Absolute Liver Weight in Female Monkeys Administered Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6 Months<sup>a\*</sup>**

Model	Test for Significant Difference <i>p</i> -Value <sup>b</sup>	Variance <i>p</i> -Value <sup>c</sup>	Means <i>p</i> -Value <sup>c</sup>	Scaled Residuals for Dose Group <sup>d</sup>	AIC	BMC <sub>10</sub> (mg/m <sup>3</sup> )	BMCL <sub>10</sub> (mg/m <sup>3</sup> )
<b>Nonconstant variance</b>							
Exponential (Model 2) <sup>e</sup>	0.1866	0.3394	NDr	0.1416	67.27368	270.519	98.8017
Exponential (Model 3) <sup>e</sup>	0.1866	0.3394	NDr	0.1416	67.27368	270.519	98.8017
Exponential (Model 4) <sup>e</sup>	0.1866	0.3394	NDr	0.2317	73.45937	137.851	0.00414018
Exponential (Model 5) <sup>e</sup>	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Hill <sup>e</sup>	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Linear <sup>f</sup>	0.1866	0.3422	<0.0001	0.126	67.266113	265.999	87.3691
Polynomial (2-degree) <sup>f</sup>	0.1866	0.3422	<0.0001	0.126	67.266113	265.999	87.3691
Polynomial (3-degree) <sup>f</sup>	0.1866	0.3422	<0.0001	0.126	67.266113	265.994	87.3691
Power <sup>e</sup>	0.1866	0.3394	<0.0001	0.126	67.266113	265.998	87.3691

<sup>a</sup>[Leong and Torkelson \(1970\)](#); [Hazleton Laboratories \(1967\)](#).

<sup>b</sup>Values >0.05 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Values <0.10 fail to meet conventional goodness-of-fit criteria.

<sup>d</sup>Scaled residuals at concentrations closest to BMC.

<sup>e</sup>Power restricted to ≥1.

<sup>f</sup>Coefficients restricted to be negative.

\*No model was selected. Neither the constant nor nonconstant variance models provide adequate fit to the variance data.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMC<sub>10</sub> = benchmark concentration 10% extra risk; BMCL<sub>10</sub> = 95% benchmark concentration lower confidence limit; NDr = not determined.

### **Model Predictions for Increased Relative Liver Weight in Female Monkeys Treated with Vinyl Bromide via Inhalation for 6 Months**

The procedure outlined above for continuous data was applied to the data for increased relative liver weight in female monkeys treated with vinyl bromide via inhalation for 6 months ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#)). The BMD modeling results are summarized in Table C-3 and Figure C-1. The constant variance model provided adequate fit to the variance data, and adequate fit to the means was provided by all models except for the Exponential 4 and 5 models and the Hill model. The BMCLs for the models providing adequate fit are sufficiently close (i.e., differ by <threefold), so the model with the lowest AIC (Linear, Polynomial 2 and 3, Power) is selected. For relative liver weight, the BMCL<sub>10</sub> of 103.0 mg/kg-day from this model is selected.

**Table C-3. Modeling Results for Increased Relative Liver Weight in Female Monkeys Administered Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6 Months<sup>a</sup>**

Model	Test for Significant Difference <i>p</i> -Value <sup>b</sup>	Variance <i>p</i> -Value <sup>c</sup>	Means <i>p</i> -Value <sup>c</sup>	Scaled Residuals for Dose Group <sup>d</sup>	AIC	BMC <sub>10</sub> (mg/m <sup>3</sup> )	BMCL <sub>10</sub> (mg/m <sup>3</sup> )
<b>Constant variance</b>							
Exponential (Model 2) <sup>e</sup>	0.5182	0.6817	0.2367	0.9532	-0.5308398	322.982	121.181
Exponential (Model 3) <sup>e</sup>	0.5182	0.6817	0.2367	0.9532	-0.5308398	322.982	121.181
Exponential (Model 4) <sup>e</sup>	0.5182	0.6817	NDr	$-4.01 \times 10^{-7}$	0.3891677	9.14818	0.0159053
Exponential (Model 5) <sup>e</sup>	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Hill <sup>e</sup>	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Linear <sup>f*</sup>	0.5182	0.6817	0.2442	0.937	-0.574912	304.929	103.006
Polynomial (2-degree) <sup>f*</sup>	0.5182	0.6817	0.2442	0.937	-0.574912	304.929	103.006
Polynomial (3-degree) <sup>f*</sup>	0.5182	0.6817	0.2442	0.937	-0.574912	304.929	103.006
Power <sup>e*</sup>	0.5182	0.6817	0.2442	0.937	-0.574912	304.929	103.006

<sup>a</sup>[Leong and Torkelson \(1970\)](#); [Hazleton Laboratories \(1967\)](#).

<sup>b</sup>Values >0.05 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Values <0.10 fail to meet conventional goodness-of-fit criteria.

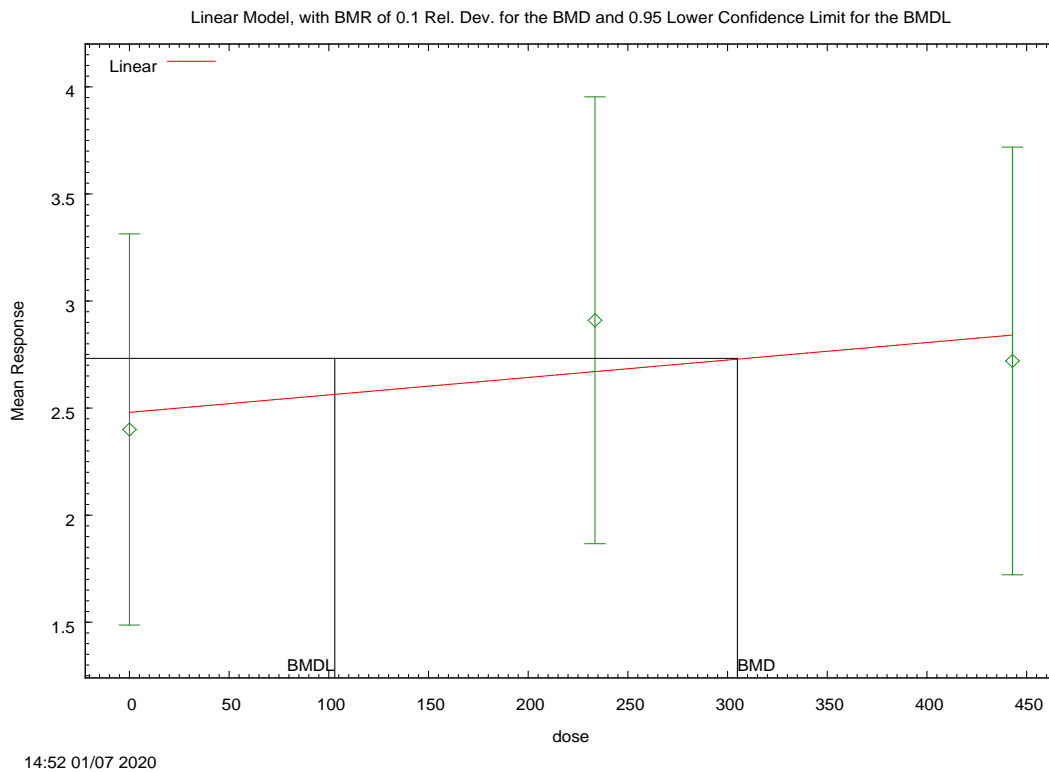
<sup>d</sup>Scaled residuals at concentrations closest to BMC.

<sup>e</sup>Power restricted to ≥1.

<sup>f</sup>Coefficients restricted to be negative.

\*Selected model. Lowest AIC among models that provided an adequate fit.

AIC = Akaike's information criterion; BMC = benchmark concentration; BMC<sub>10</sub> = benchmark concentration 10% extra risk; BMCL<sub>10</sub> = 95% benchmark concentration lower confidence limit; NDr = not determined.



**Figure C-1. Linear Model for Increased Relative Liver Weight in Female Monkeys Treated with Vinyl Bromide (CASRN 593-60-2) via Inhalation for 6 Months ([Leong and Torkelson, 1970](#); [Hazleton Laboratories, 1967](#))**

### Text Output for Figure C-1:

```
=====
      Polynomial Model. (Version: 2.21; Date: 03/14/2017)
      Input Data File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lin_increasedrelliverfm_vb_Lin-ConstantVariance-
BMR10.(d)
      Gnuplot Plotting File:
C:/Users/JKaiser/Desktop/BMDS240/Data/lin_increasedrelliverfm_vb_Lin-ConstantVariance-
BMR10.plt
                                     Wed Jan 08 15:19:32 2020
=====

BMDS Model Run
~~~~~

The form of the response function is:

Y[dose] = beta_0 + beta_1*dose + beta_2*dose^2 + ...

Dependent variable = Mean
Independent variable = Dose
rho is set to 0
Signs of the polynomial coefficients are not restricted
A constant variance model is fit
```

Total number of dose groups = 3  
 Total number of records with missing values = 0  
 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

```

alpha =      0.237777
rho =          0   Specified
beta_0 =      2.50747
beta_1 =      0.000750437
  
```

#### Asymptotic Correlation Matrix of Parameter Estimates

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

	alpha	beta_0	beta_1
alpha	1	7.7e-010	2.1e-009
beta_0	7.7e-010	1	-0.74
beta_1	2.1e-009	-0.74	1

#### Parameter Estimates

			95.0% Wald Confidence		
Interval	Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf.
Limit	alpha	0.190617	0.0852463	0.0235369	
0.357696	beta_0	2.48372	0.20525	2.08143	
2.886	beta_1	0.000814523	0.000748446	-0.000652404	
0.00228145					

#### Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	4	2.4	2.48	0.574	0.437	-0.383
233.5	3	2.91	2.67	0.42	0.437	0.937
442.9	3	2.72	2.84	0.402	0.437	-0.494

Model Descriptions for likelihoods calculated

Model A1:  $Y_{ij} = \mu(i) + e(ij)$   
 $\text{Var}\{e(ij)\} = \sigma^2$

Model A2:             $Y_{ij} = \mu(i) + e(ij)$   
                       $\text{Var}\{e(ij)\} = \sigma(i)^2$

Model A3:             $Y_{ij} = \mu(i) + e(ij)$   
                       $\text{Var}\{e(ij)\} = \sigma^2$   
                      Model A3 uses any fixed variance parameters that  
                      were specified by the user

Model R:             $Y_i = \mu + e(i)$   
                       $\text{Var}\{e(i)\} = \sigma^2$

#### Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	3.965494	4	0.069012
A2	4.348674	6	3.302651
A3	3.965494	4	0.069012
fitted	3.287456	3	-0.574912
R	2.727796	2	-1.455593

#### Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?  
           (A2 vs. R)  
 Test 2: Are Variances Homogeneous? (A1 vs A2)  
 Test 3: Are variances adequately modeled? (A2 vs. A3)  
 Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)  
 (Note: When  $\rho=0$  the results of Test 3 and Test 2 will be the same.)

#### Tests of Interest

Test	$-2 \cdot \log(\text{Likelihood Ratio})$	Test df	p-value
Test 1	3.24176	4	0.5182
Test 2	0.766361	2	0.6817
Test 3	0.766361	2	0.6817
Test 4	1.35608	1	0.2442

The p-value for Test 1 is greater than .05. There may not be a difference between responses and/or variances among the dose levels  
 Modelling the data with a dose/response curve may not be appropriate

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems to adequately describe the data

#### Benchmark Dose Computation

Specified effect =            0.1  
 Risk Type            =        Relative deviation  
 Confidence level =            0.95  
 BMD =                    304.929

BMDL = 103.006

BMDU = 1.9616e+009

## MODELING PROCEDURE FOR CANCER DATA

The model-fitting procedure for dichotomous cancer incidence is as follows. The Multistage cancer model in the U.S. 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/concentration groups including control). An adequate model fit is judged by three criteria: (1) goodness-of-fit  $p$ -value ( $p < 0.05$ ), (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) (absolute value  $< 2.0$ ). Among all of the models providing adequate fit to the data, the benchmark dose lower confidence limit (BMDL) or BMCL for the model with the lowest Akaike's information criterion (AIC) is selected as the point of departure (POD), if the BMDL/BMCLs are sufficiently close ( $< \text{threefold}$ ); if the BMDL/BMCLs are not sufficiently close ( $> \text{threefold}$ ), model-dependence is indicated, and the model with the lowest reliable BMDL/BMCL is selected. In accordance with [U.S. EPA \(2012b\)](#) and [U.S. EPA \(2005\)](#) guidance, benchmark dose (BMD) or concentration (BMC) and BMDL/BMCL values associated with an extra risk of 10% are calculated, which should be within the observable range of increased risk in a cancer bioassay. Modeling is performed for each individual tumor type with at least a statistically significant trend. Where applicable, the MS Combo model is used to evaluate the combined cancer risk of multiple tumor types. MS Combo is run using the incidence data for the individual tumor types and the polynomial degrees identified in the model runs for the individual tumor types.

### Dropping the High Dose/Concentration

In the absence of a mechanistic understanding of the biological response to a toxic agent, data from exposures much higher than the study lowest-observed-adverse-effect level (LOAEL) do not provide reliable information regarding the shape of the response at low doses/concentrations. Such exposures, however, can have a strong effect on the shape of the fitted model in the low-dose/concentration region of the dose-response curve. Thus, if lack of fit is due to characteristics of the dose-response data for high doses/concentrations, then the *Benchmark Dose Technical Guidance* document allows for data to be adjusted by eliminating the high-dose/concentration group ([U.S. EPA, 2012b](#)). Because the focus of BMD/BMC analysis is on the low-dose/concentration regions of the response curve, elimination of the high-dose/concentration group may be reasonable for certain data sets.

## BMD MODELING TO IDENTIFY POTENTIAL POINTS OF DEPARTURE FOR THE DERIVATION OF A PROVISIONAL INHALATION UNIT RISK

Six data sets from one study provided dose-response information for carcinogenicity of vinyl bromide, including incidence of angiosarcoma, hepatocellular tumors (combined), and Zymbal gland squamous cell carcinomas in males and females ([Benya et al., 1982](#)). These data are shown in Table B-13. The data sets modeled include all animals in the study, including 6-month interim sacrifices (5/sex/group), 12- and 18-month interim sacrifices (10/sex/group per



time point), and terminal sacrifices (18 months for high-concentration group, 24 months for remaining groups), as well as all animals that died or were sacrificed moribund during the study.

### **Increased Incidence of Angiosarcoma in Male S-D Rats Exposed to Vinyl Bromide via Inhalation for up to 24 Months**

The procedure outlined above for dichotomous cancer data was applied to the data for increased incidence of angiosarcoma in male rats exposed to vinyl bromide via inhalation 6 hours/day, 5 days/week, for up to 24 months ([Benya et al., 1982](#)). The data are shown in Table B-13. Table C-4 summarizes the BMD modeling results. The Multistage models did not provide statistical fit to the full data set. The characteristics of the dose-response data for high concentrations affected the shape of the model in the low-concentration region of the dose-response curve; therefore, the highest concentration was dropped from the modeled data set. With the highest concentration dropped, the Multistage models still did not provide statistical fit. With the two highest concentrations dropped, the Multistage models provided adequate statistical fit to the data. The 10% benchmark concentration lower confidence limit (BMCL<sub>10</sub>) values were sufficiently close ( $\leq$ threefold), so the model with the lowest AIC was selected (Multistage 1-degree). Figure C-2 shows the fit of the 1-degree Multistage model to the data. Based on human equivalent concentrations (HECs), the BMC<sub>10</sub> and BMCL<sub>10</sub> for angiosarcoma in male rats were 12 and 9.6 mg/m<sup>3</sup>, respectively.

**Table C-4. BMD Modeling Results for Incidence of Angiosarcoma in Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months<sup>a</sup>**

Model	DF	$\chi^2$	$\chi^2$ Goodness-of-Fit <i>p</i> -Value <sup>b</sup>	Scaled Residual at Concentration Nearest BMC	AIC	BMC <sub>10</sub> (mg/m <sup>3</sup> , HEC)	BMCL <sub>10</sub> (mg/m <sup>3</sup> , HEC)
<b>Full data set</b>							
Multistage cancer (1-degree) <sup>c</sup>	3	110.41	0	7.29	648.054	191.985	141.434
Multistage cancer (2-degree) <sup>c</sup>	3	110.41	0	7.29	648.054	191.985	141.434
Multistage cancer (3-degree) <sup>c</sup>	3	110.41	0	7.29	648.054	191.985	141.434
Multistage cancer (4-degree) <sup>c</sup>	3	110.41	0	7.29	648.054	191.985	141.434
<b>High concentration dropped</b>							
Multistage cancer (1-degree) <sup>c</sup>	3	18.37	0.0004	1.329	384.804	21.6774	18.4577
Multistage cancer (2-degree) <sup>c</sup>	3	18.37	0.0004	1.329	384.804	21.6774	18.4577
Multistage cancer (3-degree) <sup>c</sup>	3	18.37	0.0004	1.329	384.804	21.6774	18.4577
<b>Two highest concentrations dropped</b>							
Multistage cancer (1-degree) <sup>c*</sup>	2	0.04	0.9805	-0.18	202.013	12.2813	9.64194
Multistage cancer (2-degree) <sup>c</sup>	1	0	1	0	203.973	12.9663	9.65864

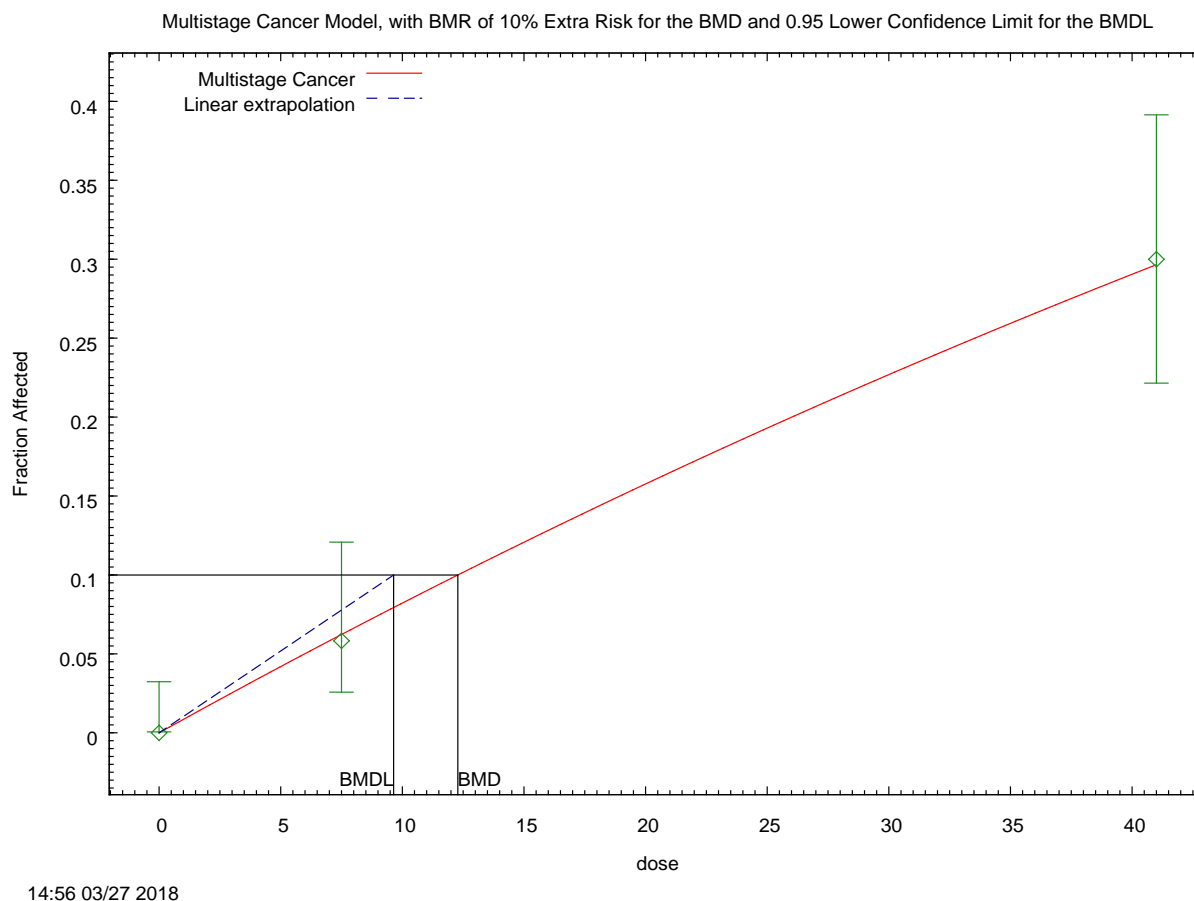
<sup>a</sup>[Benya et al. \(1982\)](#).

<sup>b</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Coefficients restricted to be positive.

\*Selected model. The Multistage models did not provide statistical fit to the full data set, or the data set with the highest concentration dropped. With two highest concentrations dropped, both models provided adequate fit. The BMCLs were sufficiently close (within threefold), so the model with the lower AIC was selected (1-degree Multistage).

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., <sub>10</sub> = concentration associated with 10% extra risk); BMD = benchmark dose; BMR = benchmark response; DF = degree(s) of freedom; HEC = human equivalent concentration; S-D = Sprague-Dawley.



**Figure C-2. Fit of the Multistage (1-Degree) Model (Two Highest Concentrations Dropped) to Data for Incidence of Angiosarcoma in Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months ([Benya et al., 1982](#))**

**Text Output for Figure C-2:**

```
=====

Multistage Model. (Version: 3.4; Date: 05/02/2014)
Input Data File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/Angiosarcoma/male/msc_angiomale2HDD_Msc1-BMR10.(d)
Gnuplot Plotting File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/Angiosarcoma/male/msc_angiomale2HDD_Msc1-BMR10.plt
                                   Tue Mar 27 14:56:36 2018
=====
BMDS_Model_Run
~~~~~

The form of the probability function is:

P[response] = background + (1-background)*[1-EXP(
               -betal*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  
Beta(1) = 0.00874614

#### 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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Beta(1)	0.00857893	0.00131396	0.00600361	0.0111542

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	-99.9865	3			
Fitted model	-100.007	1	0.0401331	2	0.9801
Reduced model	-134.643	1	69.3134	2	<.0001

AIC: 202.013

#### Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	144.000	0.000
7.5000	0.0623	7.478	7.000	120.000	-0.180
41.0000	0.2965	35.584	36.000	120.000	0.083

Chi^2 = 0.04              d.f. = 2              P-value = 0.9805

#### Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95

BMD = 12.2813  
BMDL = 9.64194  
BMDU = 15.9724

Taken together, (9.64194, 15.9724) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.0103714

### **Increased Incidence of Angiosarcoma in Female S-D Rats Exposed to Vinyl Bromide via Inhalation for up to 24 Months**

The procedure outlined above for dichotomous cancer data was applied to the data for increased incidence of angiosarcoma in female rats exposed to vinyl bromide via inhalation 6 hours/day, 5 days/week, for up to 24 months ([Benya et al., 1982](#)). The data are shown in Table B-13. Table C-5 summarizes the BMD modeling results. The Multistage models did not provide statistical fit to the full data set. The characteristics of the dose-response data for high concentrations affected the shape of the model in the low-concentration region of the dose-response curve; therefore, the highest concentration was dropped from the modeled data set. With the highest concentration dropped, the Multistage models, again, did not provide statistical fit. With the two highest concentrations dropped, only the 1-degree Multistage model provided adequate statistical fit to the data. Figure C-3 shows the fit of the 1-degree Multistage model to the data. Based on HECs, the BMC<sub>10</sub> and BMCL<sub>10</sub> for angiosarcoma in female rats were 8.4 and 6.8 mg/m<sup>3</sup>, respectively.

**Table C-5. BMD Modeling Results for Incidence of Angiosarcoma in Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months<sup>a</sup>**

Model	DF	$\chi^2$	$\chi^2$ Goodness-of-Fit <i>p</i> -Value <sup>b</sup>	Scaled Residual at Concentration Nearest BMC	AIC	BMC <sub>10</sub> (mg/m <sup>3</sup> , HEC)	BMCL <sub>10</sub> (mg/m <sup>3</sup> , HEC)
<b>Full data set</b>							
Multistage cancer (1-degree) <sup>c</sup>	3	119.92	0	6.364	701.49	272.651	185.106
Multistage cancer (2-degree) <sup>c</sup>	3	119.92	0	6.364	701.49	272.651	185.106
Multistage cancer (3-degree) <sup>c</sup>	3	119.92	0	6.364	701.49	272.651	185.106
Multistage cancer (4-degree) <sup>c</sup>	3	119.92	0	6.364	701.49	272.651	185.106
<b>Highest concentration dropped</b>							
Multistage cancer (1-degree) <sup>c</sup>	2	41.08	0	0.638	451.889	20.5342	17.0289
Multistage cancer (2-degree) <sup>c</sup>	2	41.08	0	0.638	451.889	20.5342	17.0289
Multistage cancer (3-degree) <sup>c</sup>	2	41.08	0	0.638	451.889	20.5342	17.0289
<b>Two highest concentrations dropped</b>							
Multistage cancer (1-degree) <sup>c*</sup>	1	0.27	0.6017	-0.467	248.061	8.37103	6.76577
Multistage cancer (2-degree) <sup>c</sup>	0	0	NA	0	249.78	9.73228	6.84033

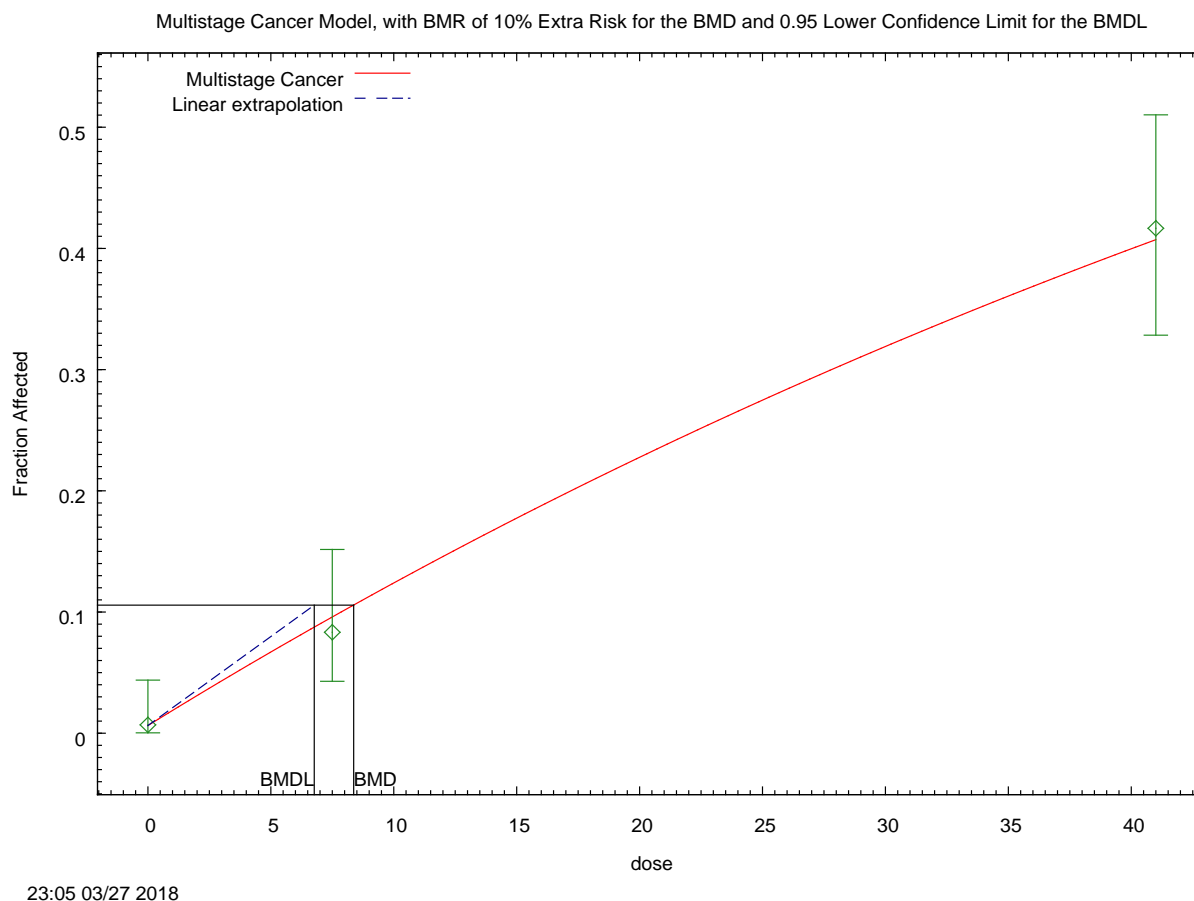
<sup>a</sup>[Benya et al. \(1982\)](#).

<sup>b</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Coefficients restricted to be positive.

\*Selected model. The Multistage models did not provide statistical fit to the full data set or the data set with the highest concentration dropped. With the two highest concentrations dropped, only the 1-degree multistage model provided adequate fit.

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., <sub>10</sub> = concentration associated with 10% extra risk); BMD = benchmark dose; BMR = benchmark response; DF = degree(s) of freedom; HEC = human equivalent concentration; NA = not applicable; S-D = Sprague-Dawley.



**Figure C-3. Fit of the Multistage (1-Degree) Model (Two Highest Concentrations Dropped) to Data for Incidence of Angiosarcoma in Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months ([Benya et al., 1982](#))**

### Text Output for Figure C-3:

```
=====
Multistage Model. (Version: 3.4; Date: 05/02/2014)
Input Data File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/Angiosarcoma/female/msc_angiofemale2HDD_Msc1-BMR10.(d)
Gnuplot Plotting File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/Angiosarcoma/female/msc_angiofemale2HDD_Msc1-BMR10.plt
Tue Mar 27 23:05:24 2018
=====
```

BMDS\_Model\_Run

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \exp(-\text{beta1} * \text{dose}^1)]$$

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  
Beta(1) = 0.0131334

#### Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.15
Beta(1)	-0.15	1

#### Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0.00637629	0.00628501	-0.0059421	0.0186947
Beta(1)	0.0125863	0.00169542	0.00926336	0.0159093

#### Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-121.89	3			
Fitted model	-122.03	2	0.281245	1	0.5959
Reduced model	-168.102	1	92.4238	2	<.0001

AIC: 248.061

#### Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0064	0.918	1.000	144.000	0.086
7.5000	0.0959	11.506	10.000	120.000	-0.467
41.0000	0.4069	48.831	50.000	120.000	0.217

Chi^2 = 0.27      d.f. = 1      P-value = 0.6017

#### Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 8.37103  
BMDL = 6.76577  
BMDU = 10.556

Taken together, (6.76577, 10.556 ) is a 90 % two-sided confidence



interval for the BMD

Cancer Slope Factor = 0.0147803

### **Increased Incidence of Hepatocellular Neoplasms in Male S-D Rats Exposed to Vinyl Bromide via Inhalation for up to 24 Months**

The procedure outlined above for dichotomous cancer data, was applied to the data for increased incidence of hepatocellular neoplasms in male rats exposed to vinyl bromide via inhalation 6 hours/day, 5 days/week, for up to 24 months ([Benya et al., 1982](#)). The data are shown in Table B-13. Table C-6 summarizes the BMD modeling results. The Multistage models did not provide statistical fit to the full data set. The characteristics of the dose-response data for high concentrations affected the shape of the model in the low-concentration region of the dose-response curve; therefore, the highest concentration was dropped from the data set. With the highest concentration dropped, all models converged on the 1-degree Multistage model and provided an adequate fit. Figure C-4 shows the fit of the 1-degree Multistage model to the data. Based on HECs, the BMC<sub>10</sub> and BMCL<sub>10</sub> for hepatocellular neoplasms in male rats were 240 and 130 mg/m<sup>3</sup>, respectively.

**Table C-6. BMD Modeling Results for Incidence of Hepatocellular Neoplasms in Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months<sup>a</sup>**

Model	DF	$\chi^2$	$\chi^2$ Goodness-of-Fit <i>p</i> -Value <sup>b</sup>	Scaled Residual at Concentration Nearest BMC	AIC	BMC <sub>10</sub> (mg/m <sup>3</sup> , HEC)	BMCL <sub>10</sub> (mg/m <sup>3</sup> , HEC)
<b>Full data set</b>							
Multistage cancer (1-degree) <sup>c</sup>	4	9.51	0.0496	NA	280.342	NA	NA
Multistage cancer (2-degree) <sup>c</sup>	4	9.51	0.0496	NA	280.342	NA	NA
Multistage cancer (3-degree) <sup>c</sup>	4	9.51	0.0496	NA	280.342	NA	NA
Multistage cancer (4-degree) <sup>c</sup>	4	9.51	0.0496	NA	280.342	NA	NA
<b>High concentration dropped</b>							
Multistage cancer (1-degree) <sup>c*</sup>	2	2.21	0.3306	-0.372	233.652	241.299	131.437
Multistage cancer (2-degree) <sup>c</sup>	2	2.21	0.3306	-0.372	233.652	241.299	131.437
Multistage cancer (3-degree) <sup>c</sup>	2	2.21	0.3306	-0.372	233.652	241.299	131.437

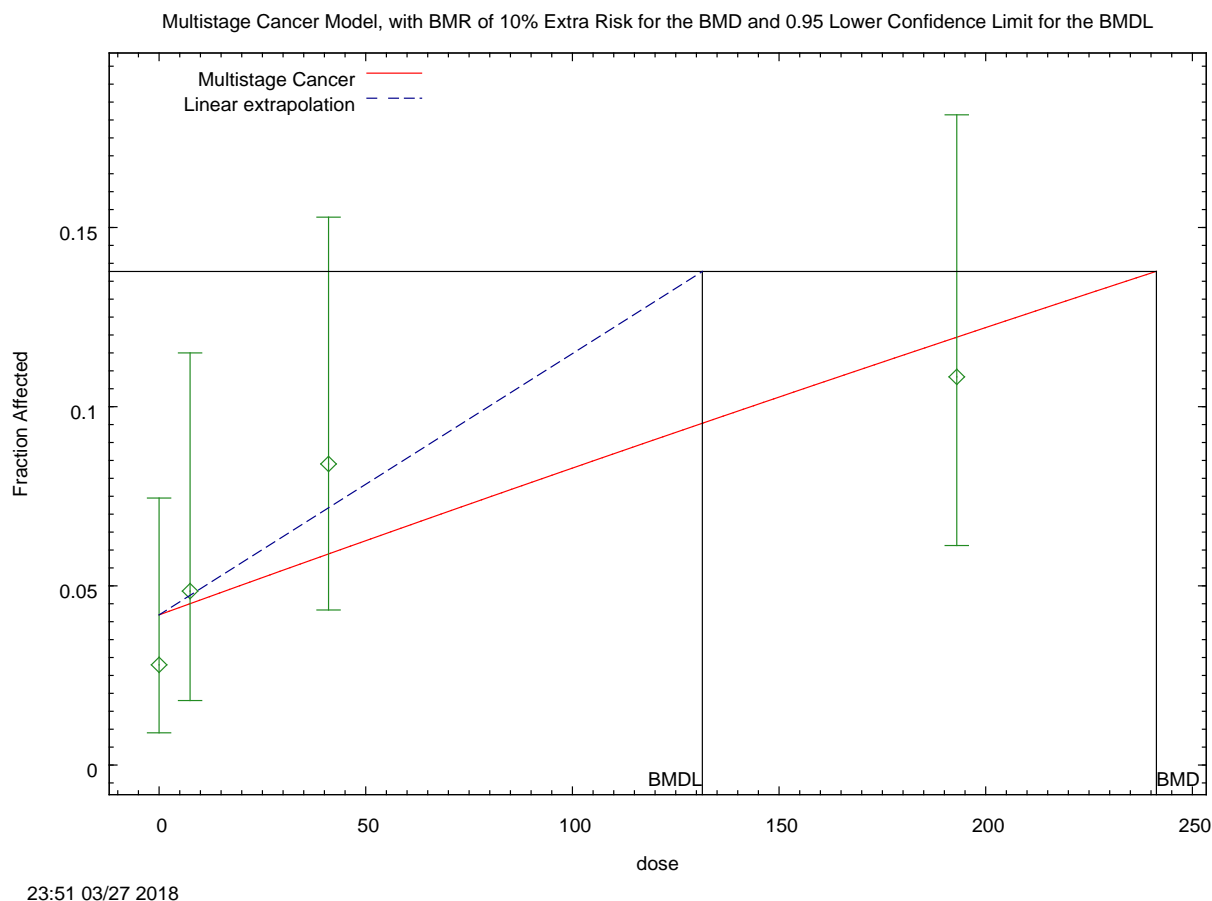
<sup>a</sup>[Benya et al. \(1982\)](#).

<sup>b</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Coefficients restricted to be positive.

\*Selected model. The Multistage models did not provide statistical fit to the full data set. With highest concentration dropped, the 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model.

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., <sub>10</sub> = concentration associated with 10% extra risk); BMD = benchmark dose; BMR = benchmark response; DF = degree(s) of freedom; HEC = human equivalent concentration; NA = not applicable (e.g., BMD computation failed); S-D = Sprague-Dawley.



**Figure C-4. Fit of the Multistage (1-Degree) Model (Highest Concentration Dropped) to Data for Incidence of Hepatocellular Neoplasms in Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months ([Benya et al., 1982](#))**

#### Text Output for Figure C-4:

```
=====
Multistage Model. (Version: 3.4; Date: 05/02/2014)
Input Data File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/hepatictumor/msc_heptumormaleHDD_Msc1-BMR10.(d)
Gnuplot Plotting File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/hepatictumor/msc_heptumormaleHDD_Msc1-BMR10.plt
Tue Mar 27 23:51:47 2018
=====
BMDS_Model_Run
=====
```

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = Effect

Independent variable = Dose

Total number of observations = 4  
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 = 0.046367  
Beta(1) = 0.000375425

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.54
Beta(1)	-0.54	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0.0419259	0.0126693	0.0170945	0.0667572
Beta(1)	0.000436638	0.000201586	4.15369e-005	0.00083174

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-113.748	4			
Fitted model	-114.826	2	2.15674	2	0.3402
Reduced model	-117.91	1	8.32362	3	0.03978

AIC: 233.652

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0419	5.995	4.000	143.000	-0.833
7.5000	0.0451	4.641	5.000	103.000	0.171
41.0000	0.0589	7.012	10.000	119.000	1.163
193.0000	0.1194	14.323	13.000	120.000	-0.372

Chi^2 = 2.21      d.f. = 2      P-value = 0.3306

Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 241.299  
BMDL = 131.437  
BMDU = 781.464

Taken together, (131.437, 781.464) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.000760821

### **Increased Incidence of Hepatocellular Neoplasms in Female S-D Rats Exposed to Vinyl Bromide via Inhalation for up to 24 Months**

The procedure outlined above for dichotomous cancer data was applied to the data for increased incidence of hepatocellular neoplasms in female rats exposed to vinyl bromide via inhalation 6 hours/day, 5 days/week, for up to 24 months ([Benya et al., 1982](#)). The data are shown in Table B-13. Table C-7 summarizes the BMD modeling results. The Multistage models did not provide statistical fit to the full data set. The characteristics of the dose-response data for high concentrations affected the shape of the model in the low-concentration region of the dose-response curve; therefore, the highest concentration was dropped from the modeled data set. With the highest concentration dropped, the Multistage models, again, did not provide statistical fit. No further concentrations could be dropped from the data set because there was no statistical significance at the next highest concentration; therefore, no model was selected.

**Table C-7. BMD Modeling Results for Incidence of Hepatocellular Neoplasms in Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months<sup>a</sup>**

Model	DF	$\chi^2$	$\chi^2$ Goodness-of-Fit <i>p</i> -Value <sup>b</sup>	Scaled Residual at Concentration Nearest BMC	AIC	BMC <sub>10</sub> (mg/m <sup>3</sup> , HEC)	BMCL <sub>10</sub> (mg/m <sup>3</sup> , HEC)
<b>Full data set</b>							
Multistage cancer (1-degree) <sup>c</sup>	4	16.07	0.0029	NA	418.626	NA	NA
Multistage cancer (2-degree) <sup>c</sup>	4	16.07	0.0029	NA	418.626	NA	NA
Multistage cancer (3-degree) <sup>c</sup>	4	16.07	0.0029	NA	418.626	NA	NA
Multistage cancer (4-degree) <sup>c</sup>	4	16.07	0.0029	NA	418.626	NA	NA
<b>High concentration dropped</b>							
Multistage cancer (1-degree) <sup>c</sup>	2	10.61	0.005	-0.055	351.64	209.9	109.954
Multistage cancer (2-degree) <sup>c</sup>	2	10.61	0.005	-0.055	351.64	209.9	109.954
Multistage cancer (3-degree) <sup>c</sup>	2	10.61	0.005	-0.055	351.64	209.9	109.954

<sup>a</sup>[Benya et al. \(1982\)](#).

<sup>b</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Coefficients restricted to be positive.

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., <sub>10</sub> = concentration associated with 10% extra risk); BMD = benchmark dose; BMR = benchmark response; DF = degree(s) of freedom; HEC = human equivalent concentration; NA = not applicable (e.g., BMD computation failed); S-D = Sprague-Dawley.

### Increased Incidence of Zymbal Gland Carcinomas in Male S-D Rats Exposed to Vinyl Bromide via Inhalation for up to 24 Months

The procedure outlined above for dichotomous cancer data was applied to the data for increased incidence of Zymbal gland carcinomas in male rats exposed to vinyl bromide via inhalation 6 hours/day, 5 days/week, for up to 24 months ([Benya et al., 1982](#)). The data are shown in Table B-13. Table C-8 summarizes the BMD modeling results. The Multistage models all converged on the 1-degree Multistage model and provided statistical fit to the data. Figure C-5 shows the fit of the 1-degree Multistage model to the data. Based on HECs, the BMC<sub>10</sub> and BMCL<sub>10</sub> for Zymbal gland carcinomas in male rats were 270 and 210 mg/m<sup>3</sup>, respectively.

<b>Table C-8. BMD Modeling Results for Incidence of Zymbal Gland Carcinomas in Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months<sup>a</sup></b>							
<b>Model</b>	<b>DF</b>	<b><math>\chi^2</math></b>	<b><math>\chi^2</math> Goodness-of-Fit <i>p</i>-Value<sup>b</sup></b>	<b>Scaled Residual at Concentration Nearest BMC</b>	<b>AIC</b>	<b>BMC<sub>10</sub> (mg/m<sup>3</sup>, HEC)</b>	<b>BMCL<sub>10</sub> (mg/m<sup>3</sup>, HEC)</b>
<b>Full data set</b>							
Multistage cancer (1-degree) <sup>c*</sup>	3	3.33	0.344	1.282	274.156	272.836	213.703
Multistage cancer (2-degree) <sup>c</sup>	3	3.33	0.344	1.282	274.156	272.836	213.703
Multistage cancer (3-degree) <sup>c</sup>	3	3.33	0.344	1.282	274.156	272.836	213.703
Multistage cancer (4-degree) <sup>c</sup>	3	3.33	0.344	1.282	274.156	272.836	213.703

<sup>a</sup>[Benya et al. \(1982\)](#).

<sup>b</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

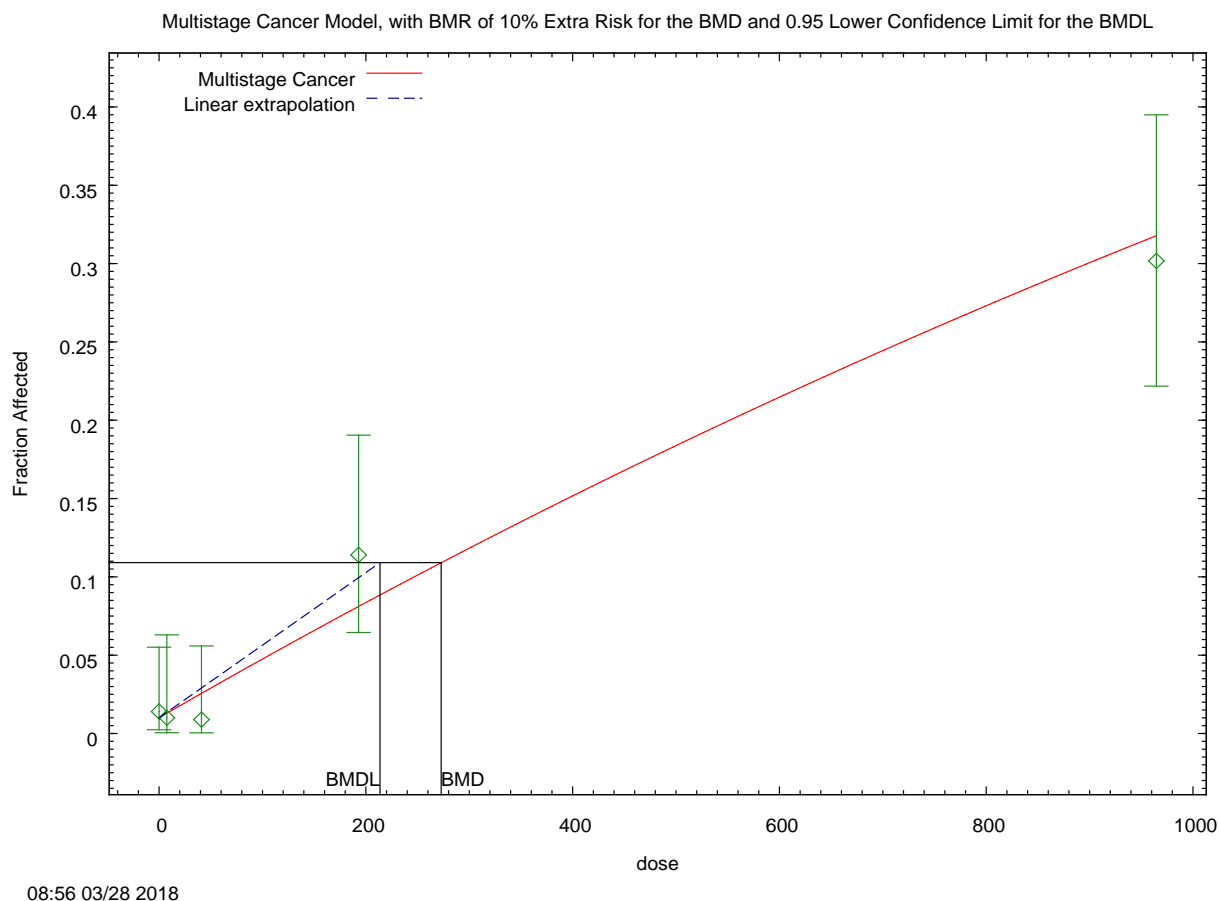
<sup>c</sup>Coefficients restricted to be positive.

\*Selected model. The 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model.

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR:

i.e., <sub>10</sub> = concentration associated with 10% extra risk); BMD = benchmark dose; BMR = benchmark response;

DF = degree(s) of freedom; HEC = human equivalent concentration; S-D = Sprague-Dawley.



**Figure C-5. Fit of the Multistage (1-Degree) Model to Data for Incidence of Zymbal Gland Carcinomas in Male S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months ([Benya et al., 1982](#))**

**Text Output for Figure C-5:**

```
=====
Multistage Model. (Version: 3.4; Date: 05/02/2014)
Input Data File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/zymbaltumor/male/msc_zymbaltumormale_Msc1-BMR10.(d)
Gnuplot Plotting File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/zymbaltumor/male/msc_zymbaltumormale_Msc1-BMR10.plt
Wed Mar 28 08:56:32 2018
=====
```

BMDS\_Model\_Run

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^1)]$$

The parameter betas are restricted to be positive



Dependent variable = Effect  
Independent variable = Dose

Total number of observations = 5  
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 = 0.0150035  
Beta(1) = 0.000363103

#### Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.24
Beta(1)	-0.24	1

#### Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0.0101462	0.0060259	-0.00166437	0.0219567
Beta(1)	0.000386168	6.04509e-005	0.000267687	0.00050465

#### Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-133.299	5			
Fitted model	-135.078	2	3.5572	3	0.3134
Reduced model	-175.29	1	83.9811	4	<.0001

AIC: 274.156

#### Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0101	1.441	2.000	142.000	0.468
7.5000	0.0130	1.288	1.000	99.000	-0.255
41.0000	0.0257	2.878	1.000	112.000	-1.121
193.0000	0.0812	9.261	13.000	114.000	1.282
964.6000	0.3180	36.886	35.000	116.000	-0.376

Chi^2 = 3.33      d.f. = 3      P-value = 0.3440

#### Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 272.836

BMDL = 213.703

BMDU = 358.816

Taken together, (213.703, 358.816) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.000467939

### Increased Incidence of Zymbal Gland Carcinomas in Female S-D Rats Exposed to Vinyl Bromide via Inhalation for up to 24 Months

The procedure outlined above for dichotomous cancer data was applied to the data for increased incidence of Zymbal gland carcinomas in female rats exposed to vinyl bromide via inhalation 6 hours/day, 5 days/week, for up to 24 months ([Benya et al., 1982](#)). The data are shown in Table B-13. Table C-9 summarizes the BMD modeling results. The Multistage models all converged on a 1-degree Multistage model and provided statistical fit to the data. Figure C-6 shows the fit of the 1-degree Multistage model to the data. Based on HECs, the BMC<sub>10</sub> and BMCL<sub>10</sub> for Zymbal gland carcinomas in female rats were 1,000 and 620 mg/m<sup>3</sup>, respectively.

<b>Table C-9. BMD Modeling Results for Incidence of Zymbal Gland Carcinomas in Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months<sup>a</sup></b>							
<b>Model</b>	<b>DF</b>	<b><math>\chi^2</math></b>	<b><math>\chi^2</math> Goodness-of-Fit <i>p</i>-Value<sup>b</sup></b>	<b>Scaled Residual at Concentration Nearest BMC</b>	<b>AIC</b>	<b>BMC<sub>10</sub> (mg/m<sup>3</sup>, HEC)</b>	<b>BMCL<sub>10</sub> (mg/m<sup>3</sup>, HEC)</b>
<b>Full data set</b>							
Multistage cancer (1-degree) <sup>c*</sup>	3	6.39	0.0943	-0.13	129.603	995.207	621.746
Multistage cancer (2-degree) <sup>c</sup>	3	6.39	0.0943	-0.13	129.603	995.207	621.746
Multistage cancer (3-degree) <sup>c</sup>	3	6.39	0.0943	-0.13	129.603	995.206	621.746
Multistage cancer (4-degree) <sup>c</sup>	3	6.39	0.0943	-0.13	129.603	995.206	621.746

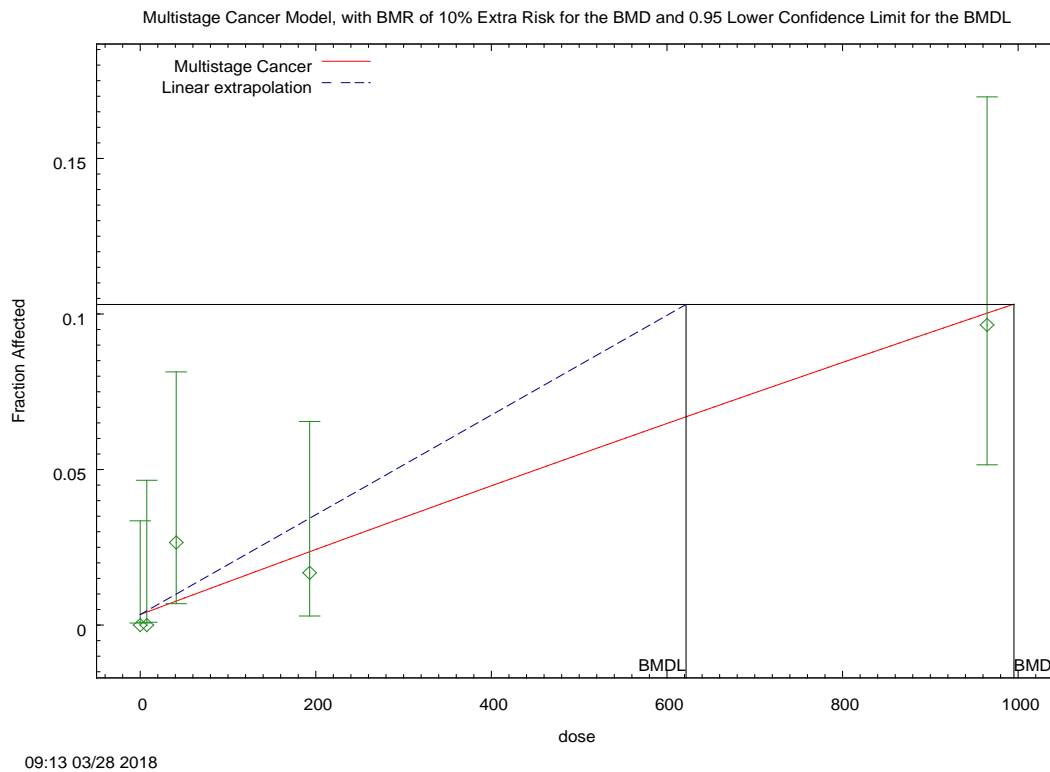
<sup>a</sup>[Benya et al. \(1982\)](#).

<sup>b</sup>Values <0.1 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Coefficients restricted to be positive.

\*Selected model. The 1-degree Multistage model provided adequate fit to the data. The higher degree polynomial models took the form of the 1-degree model.

AIC = Akaike's information criterion; BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., <sub>10</sub> = concentration associated with 10% extra risk); BMD = benchmark dose; BMR = benchmark response; DF = degree(s) of freedom; HEC = human equivalent concentration; S-D = Sprague-Dawley.



**Figure C-6. Fit of the Multistage (1-Degree) Model to Data for Incidence of Zymbal Gland Carcinomas in Female S-D Rats Exposed to Vinyl Bromide (CASRN 593-60-2) via Inhalation for up to 24 Months ([Benya et al., 1982](#))**

**Text Output for Figure C-6:**

```
=====
Multistage Model. (Version: 3.4; Date: 05/02/2014)
Input Data File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/zymbaltumor/female/msc_zymbaltumorfemale_Msc1-BMR10.(d)
Gnuplot Plotting File: C:/Users/rhoades/Desktop/PTV
BMDS/vinylbromide/zymbaltumor/female/msc_zymbaltumorfemale_Msc1-BMR10.plt
Wed Mar 28 09:13:21 2018
=====

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 = 5
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 = 0.00516248  
Beta(1) = 9.90359e-005

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.47
Beta(1)	-0.47	1

Parameter Estimates

		95.0% Wald Confidence		
Interval	Variable	Estimate	Std. Err.	Lower Conf. Limit    Upper Conf. Limit
0.0128514 0.00017175	Background	0.00339121	0.00482674	-0.00606902
	Beta(1)	0.000105868	3.3614e-005	3.99857e-005

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-60.1739	5			
Fitted model	-62.8015	2	5.25528	3	0.154
Reduced model	-73.3358	1	26.3238	4	<.0001

AIC: 129.603

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0034	0.471	0.000	139.000	-0.688
7.5000	0.0042	0.414	0.000	99.000	-0.645
41.0000	0.0077	0.871	3.000	113.000	2.290
193.0000	0.0235	2.802	2.000	119.000	-0.485
964.6000	0.1001	11.416	11.000	114.000	-0.130

Chi^2 = 6.39      d.f. = 3      P-value = 0.0943

Benchmark Dose Computation

```
Specified effect =          0.1
Risk Type        =      Extra risk
Confidence level =          0.95
      BMD =          995.207
      BMDL =          621.746
      BMDU =          1813.35
Taken together, (621.746, 1813.35) is a 90      % two-sided confidence
interval for the BMD
Cancer Slope Factor =    0.000160837
```

### **BMD Model Output for MS Combo Model of Tumors in Male S-D Rats Exposed to Vinyl Bromide via Inhalation:**

```
=====
      MS_COMBO. (Version: 1.10; Date: 01/29/2017)
      Input Data File: C:\Users\rhoades\Desktop\PTV
BMDS\vinylbromide\MSCombo\MSComboMale.(d)
      Gnuplot Plotting File: C:\Users\rhoades\Desktop\PTV
BMDS\vinylbromide\MSCombo\MSComboMale.plt
                                     Wed Mar 28 16:51:14 2018
=====
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
Data file name = angiomale2HDD.dax

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
      Beta(1) =    0.00874614

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	*	*	*
Beta(1)	0.00857892	*	*	*

\* - Indicates that this value is not calculated.

Analysis of Deviance Table					
Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-99.9865	3			
Fitted model	-100.007	1	0.0401331	2	0.9801
Reduced model	-134.643	1	69.3134	2	<.0001
AIC:	202.013				

Log-likelihood Constant 95.577776546820544

Goodness of Fit					
Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	144.000	0.000
7.5000	0.0623	7.478	7.000	120.000	-0.180
41.0000	0.2965	35.584	36.000	120.000	0.083

Chi^2 = 0.04 d.f. = 2 P-value = 0.9805

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 12.2813

BMDL = 9.64194

BMDU = 15.9724

Taken together, (9.64194, 15.9724) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0103714

```
=====
MS_COMBO. (Version: 1.10; Date: 01/29/2017)
Input Data File: C:\Users\rhoades\Desktop\PTV
BMDS\vinylbromide\MSCombo\MSComboMale.(d)
Gnuplot Plotting File: C:\Users\rhoades\Desktop\PTV
BMDS\vinylbromide\MSCombo\MSComboMale.plt
Wed Mar 28 16:51:14 2018
=====
BMDS_Model_Run
~~~~~
```

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \exp(-\text{beta1} * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = Effect  
Independent variable = Dose  
Data file name = heptumormaleHDD.dax

Total number of observations = 4  
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 = 0.046367  
Beta(1) = 0.000375425

#### Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.62
Beta(1)	-0.62	1

#### Parameter Estimates

		95.0% Wald Confidence			
Interval	Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Limit	Background	0.0419259	*	*	*
	Beta(1)	0.000436638	*	*	*

\* - Indicates that this value is not calculated.

#### Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-113.748	4			
Fitted model	-114.826	2	2.15674	2	0.3402
Reduced model	-117.91	1	8.32362	3	0.03978

AIC: 233.652

Log-likelihood Constant 106.22823536283573

#### Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0419	5.995	4.000	143.000	-0.833
7.5000	0.0451	4.641	5.000	103.000	0.171
41.0000	0.0589	7.012	10.000	119.000	1.163

```

193.0000      0.1194      14.323      13.000      120.000      -0.372
Chi^2 = 2.21      d.f. = 2      P-value = 0.3306

```

#### Benchmark Dose Computation

```

Specified effect =      0.1
Risk Type      =      Extra risk
Confidence level =      0.95
      BMD =      241.299
      BMDL =      131.437
      BMDU =      781.464

```

Taken together, (131.437, 781.464) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000760821

```

=====
      MS_COMBO. (Version: 1.10; Date: 01/29/2017)
      Input Data File: C:\Users\rhoades\Desktop\PTV
BMSD\vinylbromide\MSCombo\MSComboMale.(d)
      Gnuplot Plotting File: C:\Users\rhoades\Desktop\PTV
BMSD\vinylbromide\MSCombo\MSComboMale.plt

```

Wed Mar 28 16:51:14 2018

```

=====
BMSD_Model_Run
~~~~~

```

The form of the probability function is:

```

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

```

The parameter betas are restricted to be positive

```

Dependent variable = Effect
Independent variable = Dose
Data file name = zymbaltumormale.dax

```

```

Total number of observations = 5
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 =      0.0150035
      Beta(1) =      0.000363103

```

#### Asymptotic Correlation Matrix of Parameter Estimates

```

      Background      Beta(1)
Background      1      -0.51

```



Beta(1)            -0.51            1

#### Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0.0101462	*	*	*
Beta(1)	0.000386168	*	*	*

\* - Indicates that this value is not calculated.

#### Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-133.299	5			
Fitted model	-135.078	2	3.5572	3	0.3134
Reduced model	-175.29	1	83.9811	4	<.0001

AIC:            274.156

Log-likelihood Constant            125.34195557204099

#### Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0101	1.441	2.000	142.000	0.468
7.5000	0.0130	1.288	1.000	99.000	-0.255
41.0000	0.0257	2.878	1.000	112.000	-1.121
193.0000	0.0812	9.261	13.000	114.000	1.282
964.6000	0.3180	36.886	35.000	116.000	-0.376

Chi^2 = 3.33            d.f. = 3            P-value = 0.3440

#### Benchmark Dose Computation

Specified effect =            0.1

Risk Type            =            Extra risk

Confidence level =            0.95

BMD =            272.836

BMDL =            213.703

BMDU =            358.816

Taken together, (213.703, 358.816) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor =    0.000467939

\*\*\*\* Start of combined BMD and BMDL Calculations.\*\*\*\*

Combined Log-Likelihood            -349.91057237691183

Combined Log-likelihood Constant    327.14796748169726

#### Benchmark Dose Computation

Specified effect =            0.1

```
Risk Type           =      Extra risk
Confidence level =      0.95
      BMD =      11.2065
      BMDL =      8.94843
      BMDU =      14.2621
Multistage Cancer Slope Factor =      0.0111751
```

### **BMD Model Output for MS Combo Model of Tumors in Female S-D Rats Exposed to Vinyl Bromide via Inhalation.**

```
=====
      MS_COMBO. (Version: 1.9; Date: 05/20/2014)
      Input Data File: C:\Users\adavis10\OneDrive - Environmental
Protection Agency
(EPA)\adavis10\_BMDS_Modeling_Results\BMDS2601\Data\vinyl_bromide\female_m
scombo.(d)
      Gnuplot Plotting File: C:\Users\adavis10\OneDrive - Environmental
Protection Agency
(EPA)\adavis10\_BMDS_Modeling_Results\BMDS2601\Data\vinyl_bromide\fo
Thu Jan 16 05:50:47 2020
=====
```

#### **BMDS\_Model\_Run**

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \exp(-\text{beta1} * \text{dose}^1)]$$

The parameter betas are restricted to be positive

```
Dependent variable = Effect
Independent variable = Dose
Data file name = angio_f_2hdd.dax
```

```
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

Beta(1) = 0.0131334

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.57
Beta(1)	-0.57	1

Parameter Estimates

		95.0% Wald		
Confidence Interval	Variable	Estimate	Std. Err.	Lower Conf. Limit
Upper Conf. Limit	Background	0.00637629	*	*
*	Beta(1)	0.0125863	*	*
*				

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-121.89	3			
Fitted model	-122.03	2	0.281245	1	0.5959
Reduced model	-168.102	1	92.4238	2	<.0001

AIC: 248.061

Log-likelihood Constant 116.25058964456983

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0064	0.918	1.000	144.000	0.086
7.5000	0.0959	11.506	10.000	120.000	-0.467
41.0000	0.4069	48.831	50.000	120.000	0.217

Chi^2 = 0.27 d.f. = 1 P-value = 0.6017

# Benchmark Dose Computation

Specified effect = 0.1  
Risk Type = Extra risk  
Confidence level = 0.95  
BMD = 8.37104  
BMDL = 6.76577  
BMDU = 10.556

Taken together, (6.76577, 10.556 ) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0147803

```
=====
MS_COMBO. (Version: 1.9; Date: 05/20/2014)
Input Data File: C:\Users\adavis10\OneDrive - Environmental
Protection Agency
(EPA)\adavis10\BMDS_Modeling_Results\BMDS2601\Data\vinyl_bromide\female_m
scombo.(d)
Gnuplot Plotting File: C:\Users\adavis10\OneDrive - Environmental
Protection Agency
(EPA)\adavis10\BMDS_Modeling_Results\BMDS2601\Data\vinyl_bromide\fo
Thu Jan 16 05:50:47 2020
=====
```

## BMDS\_Model\_Run

~~~~~

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{betal} * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = Effect  
Independent variable = Dose  
Data file name = zymbal\_f\_full.dax

Total number of observations = 5  
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 = 0.00516248  
Beta(1) = 9.90359e-005

Asymptotic Correlation Matrix of Parameter Estimates

|            | Background | Beta(1) |
|------------|------------|---------|
| Background | 1          | -0.55   |
| Beta(1)    | -0.55      | 1       |

Parameter Estimates

|                     |             | 95.0% Wald |       |             |
|---------------------|-------------|------------|-------|-------------|
| Confidence Interval |             |            |       |             |
| Variable            | Estimate    | Std. Err.  | Lower | Conf. Limit |
| Upper Conf. Limit   |             |            |       |             |
| Background          | 0.00339121  | *          | *     |             |
| *                   |             |            |       |             |
| Beta(1)             | 0.000105868 | *          | *     |             |
| *                   |             |            |       |             |

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

| Model         | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---------------|-----------------|-----------|----------|-----------|---------|
| Full model    | -60.1739        | 5         |          |           |         |
| Fitted model  | -62.8015        | 2         | 5.25528  | 3         | 0.154   |
| Reduced model | -73.3358        | 1         | 26.3238  | 4         | <.0001  |

AIC: 129.603

Log-likelihood Constant 55.318204505968403

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|------|------------|----------|----------|------|-----------------|
|------|------------|----------|----------|------|-----------------|

|          |        |        |        |         |        |
|----------|--------|--------|--------|---------|--------|
| 0.0000   | 0.0034 | 0.471  | 0.000  | 139.000 | -0.688 |
| 7.5000   | 0.0042 | 0.414  | 0.000  | 99.000  | -0.645 |
| 41.0000  | 0.0077 | 0.871  | 3.000  | 113.000 | 2.290  |
| 193.0000 | 0.0235 | 2.802  | 2.000  | 119.000 | -0.485 |
| 964.6000 | 0.1001 | 11.416 | 11.000 | 114.000 | -0.130 |

Chi^2 = 6.39      d.f. = 3      P-value = 0.0943

#### Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 995.207  
 BMDL = 621.746  
 BMDU = 1813.35

Taken together, (621.746, 1813.35) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000160837

\*\*\*\* Start of combined BMD and BMDL Calculations.\*\*\*\*

Combined Log-Likelihood -184.83199235072126  
 Combined Log-likelihood Constant 171.56879415053822

#### Benchmark Dose Computation

Specified effect = 0.1  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 8.30122  
 BMDL = 6.71988

Multistage Cancer Slope Factor = 0.0148812

## APPENDIX D. REFERENCES

- Abreu, BE; Emerson, GA. (1940). Difference in inorganic bromide content of liver after anesthesia with saturated and unsaturated brominated hydrocarbons. *Univ Calif Publ Pharmacol* 1: 313-319.
- Abreu, BE; Peoples, SA; Emerson, GA. (1939). A preliminary survey of the anesthetic properties of certain halogenated hydrocarbons. *Anesth Analg* 18: 156-161.
- ACGIH (American Conference of Governmental Industrial Hygienists). (2001). Vinyl bromide. In *Documentation of the threshold limit values and biological exposure indices* (7th ed.). Cincinnati, OH.
- ACGIH (American Conference of Governmental Industrial Hygienists). (2016). Vinyl bromide [TLV/BEI]. In *2016 TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices* (pp. 61). Cincinnati, OH. <https://www.acgih.org/forms/store/ProductFormPublic/2016-tlvs-and-beis>
- Andersen, ME. (1980). A general, physiologically-based pharmacokinetic model for the metabolism of inhaled gases and vapors [Abstract]. *Toxicol Lett Spec. Issue* 1: 87.
- Andersen, ME; Gargas, ML; Jones, RA; Jenkins, LJ, Jr. (1980). Determination of the kinetic constants for metabolism of inhaled toxicants in vivo using gas uptake measurements. *Toxicol Appl Pharmacol* 54: 100-116. [http://dx.doi.org/10.1016/0041-008X\(80\)90011-3](http://dx.doi.org/10.1016/0041-008X(80)90011-3)
- ATSDR (Agency for Toxic Substances and Disease Registry). (2017). Minimal risk levels (MRLs). June 2017. Atlanta, GA: Agency for Toxic Substances and Disease Registry (ATSDR). Retrieved from <http://www.atsdr.cdc.gov/mrls/index.asp>
- Ballering, LA; Nivard, MJ; Vogel, EW. (1996). Characterization by two-endpoint comparisons of the genetic toxicity profiles of vinyl chloride and related etheno-adduct forming carcinogens in *Drosophila*. *Carcinogenesis* 17: 1083-1092. <http://dx.doi.org/10.1093/carcin/17.5.1083>
- Barbin, A; Bresil, H; Croisy, A; Jacquignon, P; Malaveille, C; Montesano, R; Bartsch, H. (1975). Liver-microsome-mediated formation of alkylating agents from vinyl bromide and vinyl chloride. *Biochem Biophys Res Commun* 67: 596-603. [http://dx.doi.org/10.1016/0006-291X\(75\)90854-2](http://dx.doi.org/10.1016/0006-291X(75)90854-2)
- Bartsch, H; Malaveille, C; Barbin, A; Planche, G. (1979a). Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues: Evidence for oxirane formation by P450-linked microsomal mono-oxygenases. *Arch Toxicol* 41: 249-277. <http://dx.doi.org/10.1007/BF00296896>
- Bartsch, H; Sabadie, N; Malaveille, C; Camus, AM; Richter-Reichhelm, HB. (1979b). Carcinogen metabolism with human and experimental animal tissues: Inter-individual and species differences. In JM Birch (Ed.), *Advances in medical oncology, research and education: Proceedings of the 12th International Cancer Congress, Buenos Aires, 1978: Volume III: Epidemiology* (pp. 179-187). Oxford, UK: Pergamon Press. <http://dx.doi.org/10.1016/B978-0-08-024386-3.50029-6>
- Belpoggi, F; Chiozzotto, D; Lauriola, M. (2012). Unsaturated halogenated hydrocarbons. In E Bingham; B Cohrssen (Eds.), *Patty's toxicology: Volume 3* (6th ed., pp. 129-229). Hoboken, NJ: John Wiley & Sons. <http://dx.doi.org/10.1002/0471435139.tox064.pub2>
- Benya, TJ; Busey, WM; Dorato, MA; Berteau, PE. (1982). Inhalation carcinogenicity bioassay of vinyl bromide in rats. *Toxicol Appl Pharmacol* 64: 367-379. [http://dx.doi.org/10.1016/0041-008X\(82\)90233-2](http://dx.doi.org/10.1016/0041-008X(82)90233-2)

- [Bolt, HM; Filser, JG; Hinderer, RK.](#) (1978). Rat liver microsomal uptake and irreversible protein binding of [1,2-14C]vinyl bromide. *Toxicol Appl Pharmacol* 44: 481-489.  
[http://dx.doi.org/10.1016/0041-008X\(78\)90256-9](http://dx.doi.org/10.1016/0041-008X(78)90256-9)
- [Bolt, HM; Filser, JG; Laib, RJ.](#) (1981). Covalent binding of haloethylenes. *Adv Exp Med Biol* 136 Pt A: 667-683. [http://dx.doi.org/10.1007/978-1-4757-0674-1\\_49](http://dx.doi.org/10.1007/978-1-4757-0674-1_49)
- [Bolt, HM; Laib, RJ; Stockle, G.](#) (1979). Formation of pre-neoplastic hepatocellular foci by vinyl bromide in newborn rats [Letter]. *Arch Toxicol* 43: 83-84.  
<http://dx.doi.org/10.1007/BF00695879>
- [CalEPA](#) (California Environmental Protection Agency). (2016). All OEHHHA acute, 8-hour and chronic reference exposure levels (chRELs) as of June 28 2016. Sacramento, CA: Office of Health Hazard Assessment. Retrieved from <http://www.oehha.ca.gov/air/allrels.html>
- [CalEPA](#) (California Environmental Protection Agency). (2017). Chemicals known to the state to cause cancer or reproductive toxicity December 29, 2017. (Proposition 65 list). Sacramento, CA: Office of Environmental Health Hazard Assessment.  
<http://oehha.ca.gov/proposition-65/proposition-65-list>
- [CalEPA](#) (California Environmental Protection Agency). (2018). OEHHHA chemical database. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from <https://oehha.ca.gov/chemicals>
- [ChemIDplus.](#) (2018a). ChemID plus advanced. Ethyl bromide, CASRN: 74-96-4. Bethesda, MD: National Institutes of Health, National Library of Medicine. Retrieved from <https://chem.nlm.nih.gov/chemidplus/rn/74-96-4>
- [ChemIDplus.](#) (2018b). ChemID plus advanced. Ethyl chloride [USP], CASRN: 75-00-3. Bethesda, MD: National Institutes of Health, National Library of Medicine. Retrieved from <https://chem.nlm.nih.gov/chemidplus/rn/75-00-3>
- [ChemIDplus.](#) (2018c). ChemID plus advanced. Vinyl chloride, CASRN: 75-01-4. Bethesda, MD: National Institutes of Health, National Library of Medicine. Retrieved from <https://chem.nlm.nih.gov/chemidplus/rn/75-01-4>
- [Conolly, RB; Jaeger, RJ.](#) (1977). Acute hepatotoxicity of ethylene and halogenated ethylenes after PCB pretreatment. *Environ Health Perspect* 21: 131-135.  
<http://dx.doi.org/10.1289/ehp.7721131>
- [Conolly, RB; Jaeger, RJ; Szabo, S.](#) (1978). Acute hepatotoxicity of ethylene, vinyl fluoride, vinyl chloride, and vinyl bromide after Aroclor 1254 pretreatment. *Exp Mol Pathol* 28: 25-33.  
[http://dx.doi.org/10.1016/0014-4800\(78\)90060-6](http://dx.doi.org/10.1016/0014-4800(78)90060-6)
- [Dorato, MA.](#) (1978). Twelve month interim report: Project number 7511-253: Volume III: Summary of gross and histopathologic observations as of study day 429 (7/26/77). New York, NY: Huntingdon Research Center.
- [Dow Chemical](#) (Dow Chemical Company). (1938). The acute vapor toxicity of vinyl bromide for rats with cover letter and attachments (sanitized). (OTS0530099. Doc #86-910000327S). Submitted under TSCA section 8D.
- [Dow Chemical](#) (Dow Chemical Company). (1969). Effects of repeated inhalation of vinyl bromide in laboratory animals with cover letter and attachments (sanitized). (OTS0530101. TSCATS/414621.). Submitted under TSCA section 8D.  
<https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0530101.xhtml>
- [Dow Chemical](#) (Dow Chemical Company). (1990). Results of range finding toxicological tests on vinyl bromide (bromoethylene) with cover letter and attachments (sanitized). (OTS0530100. 86-910000328S). Dow Chemical Company. Submitted under TSCA Section 8E.



- [ECHA](#) (European Chemicals Agency). (2018). Registered substances [bromoethylene]: Helsinki, Finland. Retrieved from <http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances>
- [EPL](#) (Experimental Pathology Laboratories). (1978). HRC project 7511-253: 18-month sacrifice: Pathology report. New City, NY: Huntingdon Research Center.
- [Ethyl Corporation](#). (1979). Letter from Ethyl Corporation to U.S. EPA regarding the enclosed results, information, and final pathology report on vinyl bromide with attachments [TSCA Submission]. (EPA/OTS Doc #88-7900281; 8EHQ-0479-0281). Richmond, VA.
- [Filser, JG; Bolt, HM](#). (1979). Pharmacokinetics of halogenated ethylenes in rats. Arch Toxicol 42: 123-136. <http://dx.doi.org/10.1007/BF00316492>
- [Filser, JG; Bolt, HM](#). (1981). Inhalation pharmacokinetics based on gas uptake studies: 1. Improvement of kinetic models. Arch Toxicol 47: 279-292.
- [Gargas, ML; Andersen, ME](#). (1982). Metabolism of inhaled brominated hydrocarbons: Validation of gas uptake results by determination of a stable metabolite. Toxicol Appl Pharmacol 66: 55-68. [http://dx.doi.org/10.1016/0041-008X\(82\)90060-6](http://dx.doi.org/10.1016/0041-008X(82)90060-6)
- [Gargas, ML; Burgess, RJ; Voisard, DE; Cason, GH; Andersen, ME](#). (1989). Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98: 87-99.
- [Gargas, ML; Seybold, PG; Andersen, ME](#). (1988). Modeling the tissue solubilities and metabolic rate constant (Vmax) of halogenated methanes, ethanes, and ethylenes. Toxicol Lett 43: 235-256. [http://dx.doi.org/10.1016/0378-4274\(88\)90031-8](http://dx.doi.org/10.1016/0378-4274(88)90031-8)
- [Guengerich, FP](#). (1981). Metabolism of vinyl halides: In vitro studies on roles of potential activated metabolites. Adv Exp Med Biol 136 Pt A: 685-692. [http://dx.doi.org/10.1007/978-1-4757-0674-1\\_50](http://dx.doi.org/10.1007/978-1-4757-0674-1_50)
- [Guengerich, FP; Kim, DH; Iwasaki, M](#). (1991). Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 4: 168-179. <http://dx.doi.org/10.1021/tx00020a008>
- [Guengerich, FP; Mason, PS; Stott, WT; Fox, TR; Watanabe, PG](#). (1981). Roles of 2-haloethylene oxides and 2-haloacetaldehydes derived from vinyl bromide and vinyl chloride in irreversible binding to protein and DNA. Cancer Res 41: 4391-4398.
- [Hazleton Laboratories](#). (1967). Effects of chronic inhalation: Vinyl bromide (final) with cover letter and attachments (sanitized). (OTS0530102. Doc #86-910000330S). Dow Chemical Company. Submitted under TSCA Section 8D.
- [HSDB](#) (Hazardous Substances Data Bank). (2009). HSDB: Vinyl bromide. CASRN: 593-60-2 [Database]. Bethesda, MD: National Library of Medicine. Retrieved from <https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+1030>
- [Huntingdon Research Center](#). (1979). Oncogenic potential of vinyl bromide during chronic inhalation exposure rats. Pathology report. Volume 1. Cincinnati, OH: National Institute for Occupational Safety and Health.
- [IARC](#) (International Agency for Research on Cancer). (1986). Some chemicals used in plastics and elastomers. Lyon, France. <http://publications.iarc.fr/57>
- [IARC](#) (International Agency for Research on Cancer). (1999). Vinyl bromide. IARC Monogr Eval Carcinog Risks Hum 71 Pt 2: 923-928.

- [IARC](#) (International Agency for Research on Cancer). (2008). 1,3-Butadiene, ethylene oxide and vinyl halides (vinyl fluoride, vinyl chloride and vinyl bromide). Lyon, France.  
<https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/1-3-Butadiene-Ethylene-Oxide-And-Vinyl-Halides-Vinyl-Fluoride-Vinyl-Chloride-And-Vinyl-Bromide--2008>
- [IARC](#) (International Agency for Research on Cancer). (2017). Agents classified by the IARC Monographs, Volumes 1-119. Lyon, France.  
[http://monographs.iarc.fr/ENG/Classification/List\\_of\\_Classifications.pdf](http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf)
- [IPCS](#) (International Programme on Chemical Safety). (2018). INCHEM: Chemical safety information from intergovernmental organizations. Geneva, Switzerland: World Health Organization, Canadian Centre for Occupational Health and Safety. Inter-Organization Programme for the Sound Management of Chemicals. Retrieved from  
<http://www.inchem.org/>
- [Kennedy, GL, Jr; Graepel, GJ.](#) (1991). Acute toxicity in the rat following either oral or inhalation exposure. *Toxicol Lett* 56: 317-326. [http://dx.doi.org/10.1016/0378-4274\(91\)90160-8](http://dx.doi.org/10.1016/0378-4274(91)90160-8)
- [Laib, RJ; Ottenwälder, H; Bolt, HM.](#) (1980). Alkylation of RNA by vinyl chloride and vinyl bromide metabolites in vivo: Effect on protein biosynthesis [Abstract]. *Naunyn-Schmiedeberg's Arch Pharmacol* 313: R63.
- [Leong, BKJ; Torkelson, TR.](#) (1970). Effects of repeated inhalation of vinyl bromide in laboratory animals with recommendations for industrial handling. *Am Ind Hyg Assoc J* 31: 1-11. <http://dx.doi.org/10.1080/0002889708506200>
- [Lijinsky, W; Andrews, AW.](#) (1980). Mutagenicity of vinyl compounds in *Salmonella typhimurium*. *Teratog Carcinog Mutagen* 1: 259-267.  
<http://dx.doi.org/10.1002/tcm.1770010303>
- [Maronpot, RR.](#) (2016). Liver [basophilic, eosinophilic, clear cell, mixed] focus. In *National Toxicology Program Nonneoplastic Lesion Atlas*. Research Triangle Park, NC: National Toxicology Program. <https://ntp.niehs.nih.gov/nnl/hepatobiliary/liver/foci/index.htm>
- [NIOSH](#) (National Institute for Occupational Safety and Health). (2016). NIOSH pocket guide to chemical hazards: Vinyl bromide. Atlanta, GA: U.S. Department of Health, Education and Welfare, Centers for Disease Control and Prevention (CDC).  
<https://www.cdc.gov/niosh/npg/npgd0657.html>
- [NTP](#) (National Toxicology Program). (2015). Final report on carcinogens background document for vinyl bromide [NTP]. (PB2015104460). Research Triangle Park, NC.  
<https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB2015104460.xhtml>
- [NTP](#) (National Toxicology Program). (2016). Vinyl halides (selected). In *Report on Carcinogens* (14 ed.). Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program.  
<https://ntp.niehs.nih.gov/ntp/roc/content/profiles/vinylhalides.pdf>
- [NTP](#) (National Toxicology Program). (2017). Vinyl bromide (593-60-2). *Chemical Effects in Biological Systems (CEBS)* (Version 3) [Database]. Research Triangle Park, NC. Retrieved from [https://manticore.niehs.nih.gov/cebssearch/test\\_article/593-60-2](https://manticore.niehs.nih.gov/cebssearch/test_article/593-60-2)
- [OSHA](#) (Occupational Safety & Health Administration). (2017a). Air contaminants: Occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC: U.S. Department of Labor.  
[https://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=STANDARDS&p\\_id=10286](https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286)

- OSHA (Occupational Safety & Health Administration). (2017b). Table Z-1: Limits for air contaminants. Occupational safety and health standards, subpart Z, toxic and hazardous substances. (OSHA standard 1910.1000, 29 CFR). Washington, DC: U.S. Department of Labor.  
[http://www.osha.gov/pls/oshaweb/owadisp.show\\_document?p\\_table=STANDARDS&p\\_id=9992](http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992)
- Ottenwälder, H; Bolt, HM. (1980). Metabolic activation of vinyl chloride and vinyl bromide by isolated hepatocytes and hepatic sinusoidal cells. *J Environ Pathol Toxicol Oncol* 4: 411-417.
- Ottenwälder, H; Laib, RJ; Bolt, HM. (1979). Alkylation of RNA by vinyl bromide metabolites in vitro and in vivo. *Arch Toxicol* 41: 279-286. <http://dx.doi.org/10.1007/BF00296897>
- Roldán-Arjona, T; García-Pedrajas, MD; Luque-Romero, FL; Hera, C; Pueyo, C. (1991). An association between mutagenicity of the ara test of salmonella typhimurium and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. *Mutagenesis* 6: 199-205. <http://dx.doi.org/10.1093/mutage/6.3.199>
- Sasaki, YF; Saga, A; Akasaka, M; Ishibashi, S; Yoshida, K; Su, YQ; Matsusaka, N; Tsuda, S. (1998). Detection in vivo genotoxicity of haloalkanes and haloalkenes carcinogenic to rodents by the alkaline single cell gel electrophoresis (comet) assay in multiple mouse organs. *Mutat Res* 419: 13-20. [http://dx.doi.org/10.1016/S1383-5718\(98\)00114-4](http://dx.doi.org/10.1016/S1383-5718(98)00114-4)
- Solomon, JJ. (1999). Cyclic adducts and intermediates induced by simple epoxides [Review]. In *IARC Scientific Publications*. Lyon, France: International Agency for Research on Cancer. <https://search.proquest.com/docview/69388579?accountid=171501>
- Swenberg, JA; Fedtke, N; Ciroussel, F; Barbin, A; Bartsch, H. (1992). Etheno adducts formed in DNA of vinyl chloride-exposed rats are highly persistent in liver. *Carcinogenesis* 13: 727-729. <http://dx.doi.org/10.1093/carcin/13.4.727>
- U.S. EPA (U.S. Environmental Protection Agency). (1984). Health and environmental effects profile for: Bromoethene (vinyl bromide) [EPA Report]. (EPA/600/X-84/143). Washington, DC.  
<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=38919#Download>
- U.S. EPA (U.S. Environmental Protection Agency). (1992). Dermal exposure assessment: Principles and applications (interim report) [EPA Report]. (EPA/600/8-91/011B). Washington, DC: Office of Health and Environmental Assessment.  
<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12188>
- U.S. EPA (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry [EPA Report]. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office.  
<https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=51174829&CFTOKEN=25006317>
- U.S. EPA (U.S. Environmental Protection Agency). (2000). Toxicological review of vinyl chloride [EPA Report]. (EPA/635R-00/004). Washington, DC.  
<http://www.epa.gov/iris/toxreviews/1001tr.pdf>
- U.S. EPA (U.S. Environmental Protection Agency). (2002). A review of the reference dose and reference concentration processes. (EPA/630/P-02/002F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum.  
<https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>

- U.S. EPA (U.S. Environmental Protection Agency). (2003). Integrated Risk Information System (IRIS) chemical assessment summary for vinyl bromide CASRN 593-60-2. Washington, DC: U.S. Environmental Protection Agency, National Center for Environmental Assessment.  
[https://cfpub.epa.gov/ncea/iris/iris\\_documents/documents/subst/0671\\_summary.pdf](https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0671_summary.pdf)
- U.S. EPA (U.S. Environmental Protection Agency). (2005). Guidelines for carcinogen risk assessment [EPA Report]. (EPA/630/P-03/001B). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum.  
[https://www.epa.gov/sites/production/files/2013-09/documents/cancer\\_guidelines\\_final\\_3-25-05.pdf](https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf)
- U.S. EPA (U.S. Environmental Protection Agency). (2011). Health effects assessment summary tables for superfund (HEAST): Bromoethene / (Vinyl Bromide) (CASRN 593-60-2) [Fact Sheet]. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. <https://epa-heast.ornl.gov/heast.php>
- U.S. EPA (U.S. Environmental Protection Agency). (2012a). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: U.S. Environmental Protection Agency, Office of Water.  
[https://rais.ornl.gov/documents/2012\\_drinking\\_water.pdf](https://rais.ornl.gov/documents/2012_drinking_water.pdf)
- U.S. EPA (U.S. Environmental Protection Agency). (2012b). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <https://www.epa.gov/risk/benchmark-dose-technical-guidance>
- U.S. EPA (U.S. Environmental Protection Agency). (2012c). Estimation Programs Interface Suite for Microsoft Windows, v 4.11: Ethene, bromo- (CASRN 593-60-2) [Fact Sheet]. Washington, DC. <https://www.epa.gov/tsca-screening-tools/epi-suite-estimation-program-interface>
- U.S. EPA (U.S. Environmental Protection Agency). (2018a). Integrated risk information system (IRIS) [Database]. Washington, DC: U.S. Environmental Protection Agency, Integrated Risk Information System. Retrieved from <http://www.epa.gov/iris/>
- U.S. EPA (U.S. Environmental Protection Agency). (2018b). The Toxic Substances Control Act's public inventory (TSCA inventory). Retrieved from <https://www.epa.gov/tsca-inventory/how-access-tsca-inventory#download>
- Van Duuren, BL. (1977). Chemical structure, reactivity, and carcinogenicity of halohydrocarbons. *Environ Health Perspect* 21: 17-23.
- Vanstee, EW; Patel, JM; Gupta, BN; Drew, RT. (1977). Consequences of vinyl bromide debromination in rat [Abstract]. *Toxicol Appl Pharmacol* 41: 175.
- Vogel, EW; Nivard, MJ. (1993). Performance of 181 chemicals in a drosophila assay predominantly monitoring interchromosomal mitotic recombination. *Mutagenesis* 8: 57-81. <http://dx.doi.org/10.1093/mutage/8.1.57>
- Wagner, VO, III; San, RH; Zeiger, E. (1992). Desiccator methodology for salmonella mutagenicity assay of vapor-phase and gas-phase test materials [Abstract]. *Environ Mol Mutagen* 19: 68.