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Provisional Peer-Reviewed Toxicity Values for

Mixtures of 1,2,3,4,5-Pentabromo-6-Chlorocyclohexane
(CASRN 87-84-3)

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,2,3,4,5-PENTABROMO-6-CHLOROCYCLOHEXANE (CASRN 87-84-3)

BACKGROUND

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

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

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

DISCLAIMERS

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

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

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

QUESTIONS REGARDING PPRTVs

Questions regarding the content of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

1,2,3,4,5-Pentabromo-6-chlorocyclohexane (PBCC), CASRN 87-84-3, is a discontinued flame retardant. The empirical formula for PBCC is $C_6H_6Br_5Cl$ (see Figure 1). PBCC is a solid at room temperature and is expected to have low solubility in water (Dow Chemical Co, 1978). A table of physicochemical properties for PBCC is provided below (see Table 1).

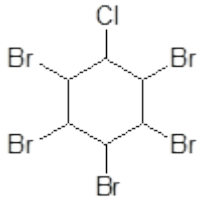

Figure 1. 1,2,3,4,5-Pentabromo-6-Chlorocyclohexane Structure

Table 1. Physicochemical Properties for PBCC (CASRN 87-84-3)

Property (unit)	Value
Boiling point (°C)	ND
Melting point (°C)	204[a]
Specific gravity (water = 1)	ND
Vapor pressure (mm Hg at 25°C)	1.16×10^{-3} (calculated)[b]
Solubility in water (mg/L)	1.2−7.0 ± 0.8[b]
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	513.09[a]

[a]Lide (2005).
[b]Dow Chemical Co (1978).

ND = no data.

Table 2 provides a summary of available toxicity values for PBCC. The Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2011a) report an oral slope factor (OSF) of 2.3×10^{-2} $(mg/kg\text{-}day)^{-1}$ for PBCC, based on tumors of the intestinal tract in rats exposed via the diet for 2 years (Dow Chemical Co, 1981).

Table 2. Summary of Available Toxicity Values for PBCC (CASRN 87-84-3)

Source (parameter)[a,b]	Value (applicability)	Notes	Reference
Noncancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST	NV	NA	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012)
ATSDR	NV	NA	ATSDR (2016)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2016a); Cal/EPA (2016b)
WHO	NV	NA	WHO (2016)
NIOSH	NV	NA	NIOSH (2015)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
ACGIH	NV	NA	ACGIH (2015)
Cancer			
IRIS	NV	NA	U.S. EPA (2016)
HEAST (OSF)	2.3×10^{-2} $(mg/kg\text{-}d)^{-1}$	Route: oral, diet; species, rat; duration, 2 yr	U.S. EPA (2011a)
DWSHA	NV	NA	U.S. EPA (2012)
NTP	NV	NA	NTP (2014)
IARC	NV	NA	IARC (2015)
Cal/EPA	NV	NA	Cal/EPA (2011); Cal/EPA (2016a); Cal/EPA (2016b)
ACGIH	NV	NA	ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: OSF = oral slope factor.

NA = not applicable; NV = not available.

Literature searches were conducted on sources published from 1900 through July 2016 for studies relevant to the derivation of provisional toxicity values for PBCC, CASRN 87-84-3. Searches were conducted using EPA's Health and Environmental Research Online (HERO) database of scientific literature. 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: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA Office of Water, U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, and OSHA.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Most of the data pertinent to the toxicity of this compound are from studies of commercial formulations that contained PBCC as the primary constituent. The nature of the mixtures and the results of the studies are described below. The available literature includes only one study (of genotoxicity) in which purified PBCC was tested (although purity of the test material was not reported). This genotoxicity study (Zeiger et al., 1992) is described in the Other Studies section (below). Unless otherwise noted, all references to pentabromochlorocyclohexane and PBCC refer to a commercial mixture of PBCC and related hexahalogenated cyclohexanes.

Commercially prepared formulations of PBCC included SE-651, which was the prototype formulation (manufactured by an unknown process), and FR-651, which was manufactured via ultraviolet bromination (Dow Chemical Co, 1980b, c). FR-651 existed in alpha, beta, or gamma steric configurations. Available toxicological data on these mixtures consist of unpublished studies on SE-651 as well as studies of various formulations of FR-651 containing predominantly the alpha isomer (FR-651A), gamma isomer (FR-651G), and an FR-651 "slurry dried" formulation. Table 3 compares the compositions of these formulations from available reports. Toxicological data were also found on formulations labelled FR-651C [Keyes et al. (1982) as cited in U.S. EPA (1985)] and FR-651P (Dow Chemical Co, 1986); however, the compositions of these formulations were not provided in the available reports, therefore they are not included in Table 3.

Table 3. Compositions of Commercial Formulations of PBCC

Compound	Percent in Formulation[a]				
	SE-651[b]	SE-651, Japanese-produced[c]	FR-651G[d]	FR-651A[e]	FR-651 "Slurry Dried"[f]
Pentabromochlorocyclohexane	65	85.3	50.3	77.25	70.7
Tetrabromodichlorocyclohexane	25	9.7	30.8	19.0	24.2
Tribromotrichlorocyclohexane	10	1.2	14.7	3.5	5.1
Dibromotetrachlorocyclohexane	–	–	4.3	0.25	0.8
Hexabromocyclohexane	–	3.8 (tentatively identified)	–	–	–

[a]Percentages may not total 100% because of unstated impurities or rounding error. Other mixtures of PBCC exist (FC-651C, FR-651P), but the compositions are unknown (Dow Chemical Co, 1986).
[b]Dow Chemical Co (1980a, 1980b, 1980c, 1980d, 1979a) reported that a detailed analysis of SE-651 was not available but that the available composition data indicated these percentages.
[c]Dow Chemical Co (1973).
[d]Dow Chemical Co (1980d).
[e]Dow Chemical Co (1980b, 1980c).
[f]Dow Chemical Co (1975).

Tables 4A and 4B provide overviews of the relevant noncancer and cancer databases for PBCC, respectively, and include all potentially relevant, repeated-dose, short-term-, subchronic-, and chronic-duration studies of mixtures containing this compound. No developmental or reproductive toxicity studies of PBCC were located in the available literature. Principal studies are identified in the table in bold font. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05, unless otherwise noted.

Table 4A. Summary of Potentially Relevant Noncancer Data for PBCC (CASRN 87-84-3)								
Category	**Number of Male/Female, Strain, Species, Test Material[a], Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								
Animal								
1. Oral (mg/kg-d)[b]								
Short-term	5 M/5 F, F344 rat, FR-651A, diet, 29 d	0, 10, 30, 100, 300, 1,000 ADD: 0, 10, 30, 100, 300, 1,000	Increased absolute liver weight in female rats	10	NA	30	TRL (1987); Dow Chemical Co (1979b) (Mechanical problems with scale affected consumption measurements; thus, the doses estimated by study authors are uncertain.)	NPR
Short-term	5 M/5 F, F344 rat, FR-651G, diet, 29 d	0, 10, 30, 100, 300, 1,000 ADD: 0, 10, 30, 100, 300, 1,000	Increased absolute liver weight in female rats	10	NA	30	Dow Chemical Co (1979a)	NPR

Table 4A. Summary of Potentially Relevant Noncancer Data for PBCC (CASRN 87-84-3)								
Category	**Number of Male/Female, Strain, Species, Test Material[a], Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Subchronic	**10 M/10 F, unspecified strain, rat, SE-651, diet, 90 d**	**0, 10, 30, 100, 300, 1,000** **ADD: 0, 10, 30, 100, 300, 1,000**	**Increased relative liver and kidney weights in both sexes; centrilobular degeneration and necrosis in livers of males at doses ≥100 mg/kg-d**	**30**	**DUB (organ weights reported as means only; lesion incidences not reported)**	**100**	**Dow Chemical Co (1990, 1960)** **(Study authors reported dose associated with histopathology of liver, but not incidences.)**	**NPR PS**
Subchronic	10 M/10 F, F344 rat, FR-651A, diet, 91 d	0, 600 ADD: 0, 600	Liver and kidney lesions in treated males and females	NDr	DUB (single dose; dose uncertain)	600	Dow Chemical Co (1980b, 1980c) (Mechanical problems with scale affected consumption measurements; thus, the doses estimated by study authors is uncertain.)	NPR

Table 4A. Summary of Potentially Relevant Noncancer Data for PBCC (CASRN 87-84-3)								
Category	**Number of Male/Female, Strain, Species, Test Material[a], Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (comments)**	**Notes[c]**
Subchronic	10 M/10 F (treated) and 15 M/15 F (control), CDF F344 rat, FR-651G, diet, 91 d	0, 10, 30, 100 ADD:0, 10, 30, 100	Liver changes (hepatocellular swelling and decreased staining intensity) in males at 100 mg/kg-d	30	DUB (doses uncertain; liver change incidences are 0% at 30 and 100% at 100)	100	Dow Chemical Co (1980d) (Mechanical problems with scale affected consumption measurements; thus, the doses estimated by authors are uncertain.)	NPR
Subchronic	10 M/10 F (treated) and 15 M/15 F (control), CDF F344 rat, FR-651 “slurry dried”, diet, 92 d	0, 90, 260, 780 ADD:0, 90, 260, 780	Liver changes (hepatocellular swelling and decreased staining intensity)	90	DUB (doses uncertain; liver change incidences are 0% at 90 and 100% at 260)	260	Dow Chemical Co (1980a) (Mechanical problems with scale affected consumption measurements; thus, the doses estimated by authors are uncertain.)	NPR

Table 4A. Summary of Potentially Relevant Noncancer Data for PBCC (CASRN 87-84-3)

Category	Number of Male/Female, Strain, Species, Test Material[a], Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Chronic	**50 M/50 F (treated) and 86 M/86 F (control), F344 rat, FR-651A, diet, 2 yr**	**0, 1, 15, 50 (M);** **0, 1, 20, 70 (F)** **ADD: 0, 1, 15, 50 (M);** **0, 1, 20, 70 (F)**	**Systemic effects: Hepatocellular hypertrophy and altered staining properties of hepatocytes, as well as increased severity of age-related, chronic-duration, progressive glomerulo nephropathy (at interim sacrifice)(at highest dose)** **Portal-of-entry effects: Lesions of the large intestine at termination (at highest dose)**	**Systemic effects: 15 (M) 20 (F)** **Portal-of-entry effects: 15 (M) 20 (F)**	**20 for intestinal lesions in male rats at termination; 45 for intestinal lesions in female rats**	**Systemic effects: 50 (M) 70 (F)** **Portal-of-entry effects: 50 (M) 70 (F)**	**Dow Chemical Co (1983a, 1983b)** **(histopathology at termination limited to gastrointestinal tract)**	**NPR, PS** **HEDs not calculated for portal-of-entry effects—intestinal lesions**
2. Inhalation (mg/m^3)								
ND								

[a]See Table 3 for test material composition information.
[b]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are presented as ADDs (mg/kg-day) for oral noncancer effects.
[c]Notes: PS = principal study; NPR = not peer reviewed.

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; DUB = data unamenable to Benchmark Dose Software; F = female(s); FEL = frank effect level; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; M = male(s); NA = not applicable; ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level.

Table 4B. Summary of Potentially Relevant Cancer Data for PBCC (CASRN 87-84-3)

Category	Number of Male/Female Species, Test Material[a], Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human								
1. Oral (mg/kg-d)								
ND								
2. Inhalation (mg/m^3)								
ND								
Animal								
1. Oral (mg/kg-d)[a]								
Chronic/ carcinogenicity	**50 M/50 F (treated) and 86 M/86 F (control), F344 rat, FR-651A, diet, 2 yr**	**0, 1, 15, 50 (M); 0, 1, 20, 70 (F)**	**Increased incidences of polypoid adenomas plus adenocarcinomas of the large intestine in males and females at the high dose**	**NA**	**5.9 for adenomas or adenocar-cinomas in females**	**NA**	**Dow Chemical Co (1983a)**	**NPR, PS Portal-of-entry effect—intestinal tumors**
Chronic/ carcinogenicity	50 M/50 F (treated) and 86 M/86 F(control), F344 rat, FR-651C, diet, 2 yr	0, 1, 15, 50 (M); 0, 1, 20, 70 (F)	Increased incidence of polypoid adenomas or adenomas plus adenocarcinomas of the large intestine in high-dose females	NA	DUB (primary report not available)	NA	Keyes et al. (1982) as cited in U.S. EPA (1985)	NPR Portal-of-entry effect−intestinal tumors
2. Inhalation (mg/m^3)								
ND								

[a]See Table 3 for test material composition information.
[b]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values for oral systemic exposures are expressed as HEDs (mg/kg-day); HED = ADD (mg/kg-day) × default DAF (U.S. EPA, 2011b).
[c]Notes: PS = principal study; NPR = not peer reviewed.

ADD = adjusted daily dose; BMCL = benchmark concentration lower confidence limit; BMDL = benchmark dose lower confidence limit; BW = body weight; DAF = dosimetric adjustment factor; DUB = data unamenable to Benchmark Dose Software; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NA = not applicable; ND = no data; NOAEL = no-observed-adverse-effect level.

HUMAN STUDIES

Oral Exposures

No studies have been identified.

Inhalation Exposures

No studies have been identified.

ANIMAL STUDIES

Oral Exposures

Overview of Animal Oral Exposure Studies

Potentially relevant data for noncancer effects come from unpublished studies of rats exposed to SE-651 for 90 days (Dow Chemical Co, 1990, 1960); to FR-651A in the diet for 29 days, 13 weeks, or 2 years (TRL, 1987; Dow Chemical Co, 1983a, b, 1980b, c, 1979b); FR-651G in the diet for 29 days or 13 weeks (Dow Chemical Co, 1980a, 1979a); and FR-651 "slurry dried" in the diet for 92 days (Dow Chemical Co, 1980a).

Short-Term-Duration Studies

TRL (1987); Dow Chemical Co (1979b)

Groups of five/sex F344 rats received FR-651A (77% PBCC) in the diet for 29 days at doses of 0, 10, 30, 100, 300, or 1,000 mg/kg-day FR-651A. The study evaluated clinical signs, body weight, serum chemistry, liver and kidney weights, and gross necropsy. No deaths nor clinical signs of toxicity were reported. Isolated occurrences of body-weight aberrations in individual treated females were reported, which the study authors suggested may have been due to a malfunction in the weighing system. Body weights of treated males did not differ from controls. A statistically significant decrease in blood urea nitrogen (BUN) was observed in females given 1,000 mg/kg-day, and a statistically significant decrease in alanine aminotransferase (ALT) occurred in males exposed to 300 or 1,000 mg/kg-day (see Table B-1); however, the toxicological significance of the decreases in BUN and ALT is uncertain. There were no treatment-related gross necropsy findings. Statistically significant increases in absolute and relative liver weights were observed in males (21 and 19%, respectively) and females (26 and 11%, respectively) treated with 1,000 mg/kg-day (see Table B-1). In addition, biologically significant elevations of absolute liver weight (>10%) were also observed in female rats exposed to 30 or 300 mg/kg-day. Considering that biologically significant increases in absolute liver weight started at 30 mg/kg-day in female rats, a lowest-observed-adverse-effect level (LOAEL) of 30 mg/kg-day is identified. The no-observed-adverse-effect level (NOAEL) is 10 mg/kg-day.

Dow Chemical Co (1979a)

Groups of F344 rats five/sex received FR-651G (50.3% PBCC) in the diet for 29 days at doses of 0, 10, 30, 100, 300, or 1,000 mg/kg-day FR-651G. Evaluations and statistical analyses were the same as in the FR-651A study (TRL, 1987; Dow Chemical Co, 1979b), except that food consumption was also measured. No deaths nor clinical signs of toxicity were reported. In males exposed to 1,000 mg/kg-day, body weight was statistically significantly decreased from Day 12 onward; terminal body weight was 21% lower than in controls. A statistically significant decrease in ALT was seen in males exposed to ≥300 mg/kg-day and in females exposed to 100 and 1,000 mg/kg-day (see Table B-2), while alkaline phosphatase (ALP) was statistically significantly decreased in females at ≥100 mg/kg-day and in males at all treatment doses except 100 mg/kg-day. The BUN was not altered in males at any dose, but BUN was statistically

significantly reduced at ≥30 mg/kg-day in females. However, the toxicological significance of decreases in BUN and the two liver enzymes is uncertain. As shown in Table B-2, absolute and relative liver and kidney weights in male rats were significantly (statistically and/or biologically) increased at doses ≥300 mg/kg-day (≥20% higher than controls). In female rats, absolute liver weights were significantly (statistically and/or biologically) increased (≥10% higher than controls) at doses ≥30 mg/kg-day, while relative liver weights were statistically significantly increased at doses ≥100 mg/kg-day. Absolute kidney weights in female rats were biologically significantly increased (≥16% higher than controls) at doses ≥100 mg/kg-day, while relative kidney weights were statistically significantly increased (12% higher than controls) at a dose of 1,000 mg/kg-day. Livers appeared darkened in 5/5 males and in 4/5 females at 1,000 mg/kg-day; 4/5 males exposed to 300 mg/kg-day also exhibited this effect (see Table B-2). A dose-related increase in the incidence of pale appearance of kidneys was reported in males exposed to ≥100 mg/kg-day (as shown in Table B-2, incidences were 2/5, 5/5, and 5/5 at the top three doses, while this effect was not observed in any control or lower dose animals). A LOAEL of 30 mg/kg-day is identified for this study based on a significant increase in absolute liver weights in females. The NOAEL is 10 mg/kg-day.

Subchronic-Duration Studies

Dow Chemical Co (1990, 1960)

SE-651was administered to groups of 10 male and 10 female rats (strain not specified) in the diet for 90 days (Dow Chemical Co, 1990, 1960). Although this report did not include the chemical composition of SE-651, a composition of 65% pentabromochlorocyclohexane, 25% tetrabromodichlorocyclohexane, and 10% tribromotrichlorocyclohexane has been ascribed to this formulation in other reports (Dow Chemical Co, 1980b, c). Dietary concentrations were reported as 0, 0.01, 0.03, 0.1, 0.3, and 1.0% pentabromochlorocyclohexane; the study authors estimated the doses as 0, 10, 30, 100, 300, and 1,000 mg/kg-day SE-651. The animals were examined "frequently" for clinical signs of toxicity. Food consumption was recorded for the first month (frequency not reported), and body weights were measured twice weekly for the first month and then weekly thereafter. Blood was collected from five females/group in the control group and the two highest dose groups for analysis of hematocrit (Hct), hemoglobin (Hb), and total and differential white blood cell (WBC) counts. The animals were sacrificed at study termination or when moribund. At sacrifice, the lungs, heart, liver, kidneys, spleen, and testes were weighed, and together with the pancreas and adrenal glands, examined microscopically.

There were no treatment-related effects on survival, clinical appearance, food consumption, or hematology at any dose (Dow Chemical Co, 1990, 1960). Male rats exhibited a statistically significant reduction in body weight (12% less than controls at termination; see Table B-3) at 1,000 mg/kg-day. No statistically or biologically significant reductions in body weight were observed in females or lower dose males. Relative liver weights (see Table B-3) were statistically significantly increased at doses ≥100 mg/kg-day in males (≥7% increase over controls) and at doses ≥300 mg/kg-day in females (≥13% increase over controls). As shown in Table B-3, relative kidney weights were also statistically significantly increased at all doses except 30 mg/kg-day in males (≥10% increase over controls) and at doses ≥300 mg/kg-day in females (≥18% increase over controls). Absolute organ weights were not reported. Histopathology findings were noted in the liver and kidneys of both sexes; however, incidences of lesions were not reported. The study authors noted that male rats exposed to ≥100 mg/kg-day exhibited centrilobular granular degeneration and necrosis, and that females exposed to ≥300 mg/kg-day exhibited bile duct epithelium proliferation, round cell infiltration periportally,

and fatty degeneration in the mid-zonal area of the liver. Fatty degeneration was also noted in the livers of male rats at 1,000 mg/kg-day. Kidney lesions consisted of interstitial and tubular nephritis at doses ≥300 mg/kg-day in both sexes, and hyaline casts (in males) or marked hydronephrosis (in females) at 1,000 mg/kg-day. A LOAEL of 100 mg/kg-day is identified for increased relative liver and kidney weights in male rats, as well as centrilobular degeneration and necrosis of the liver in males. The NOAEL is 30 mg/kg-day.

Dow Chemical Co (1980b, 1980c)

Groups of 10 CDF F344 rats/sex were fed FR-651A in the diet at target doses of 0 or 600 mg/kg-day FR-651A for 13 weeks (Dow Chemical Co, 1980b, c). Analysis of the test material indicated the composition shown in Table 5.

Table 5. Composition of FR-651A Used in Dow Chemical Co (1980b, 1980c)

Compound	Percent Composition	Percent Alpha Isomer
Pentabromochlorocyclohexane	77.25	100
Tetrabromodichlorocyclohexane	19.0	99.3
Tribromotrichlorocyclohexane	3.5	97.3
Dibromotetrachlorocyclohexane	0.25	NR

NR = not reported.

The test material was shown to be stable in the diet for at least 1 week, so diets were prepared weekly. Twice-weekly observations for clinical signs of toxicity were made, and body weight and food consumption were measured weekly. Blood samples were collected from five animals/sex/dose on Day 26, and from all animals at sacrifice, and were analyzed for BUN, ALT, and ALP. In addition, blood samples collected on Day 85 were analyzed for Hct, Hb, red blood cells (RBCs), and total and differential WBC counts. Urine was collected on Day 85 for analysis of specific gravity, pH, sugar, protein, ketones, bilirubin, and occult blood. Prior to sacrifice, the rats were subjected to ocular exams. At necropsy, the brain, heart, liver, kidneys, and testes were weighed. Additionally, most tissues (>30, including those that were weighed as well as the gastrointestinal tract and ovaries) were examined microscopically.

There were no deaths nor clinical signs of toxicity among the rats (Dow Chemical Co, 1980b, c). Treated males exhibited higher body weights than controls, with correspondingly higher food consumption rates after the fourth week on study, while body weights of treated females did not differ from controls (see Table B-4). The authors noted that "recurrent mechanical weighing problems were encountered during the study that resulted in numerous errant values." Thus, the food consumption values were examined visually and outlier values were omitted prior to statistical analysis. Whether these mechanical problems also affected body- and organ-weight measurements is uncertain because the study authors did not specifically address this question. At termination, the treated males' mean body weight was 11% higher ($p < 0.05$) than that of controls. Clinical chemistry findings in treated males and females consisted of decreases in BUN, ALP, and/or ALT (see Table B-4), but only the BUN in females and the ALP in males reached statistical significance. The toxicological significance of decreases in these parameters is uncertain. The absolute liver and kidney weights were higher in

treated animals (23 and 18%, respectively, in males; 17 and 10%, respectively, in females) than in controls; in addition, the relative liver and kidney weights were increased in males (10 and 6%, respectively), and relative liver weight was increased in females (12%). As shown in Table B-4, all treated males and females exhibited liver lesions (hepatocellular hypertrophy and decreased staining intensity of cytoplasm) that the study authors considered to be "very slight" in severity. In addition, 7/10 males exhibited "slight" hepatocellular necrosis. Kidney lesions, consisting of focal tubular degeneration and inflammation, were seen in 9/10 tested males (but not in females or controls). The only dose tested in this study, 600 mg/kg-day, is a LOAEL for liver lesions in males and females, as well as for kidney lesions in males. A NOAEL could not be identified. The effect level in this study is uncertain; as noted earlier, mechanical problems affecting food consumption measurements were reported, rendering the dose estimated by the authors uncertain.

Dow Chemical Co (1980d)

Dow Chemical Co (1980d) exposed groups of 10 CDF F344 rats/sex (15/sex controls) to FR-651G in the diet at target doses of 0, 10, 30, or 100 mg/kg-day FR-651G for 13 weeks. Analysis of the test material indicated the composition shown in Table 6.

Table 6. Analysis of FR-651G Used in Dow Chemical Co (1980d)

Compound	Percent Composition	Percent Gamma Isomer
Pentabromochlorocyclohexane	50.3	55.9
Tetrabromodichlorocyclohexane	30.8	67.9
Tribromotrichlorocyclohexane	14.7	57.1
Dibromotetrachlorocyclohexane	4.3	53.5

[a]Percent composition: Column totals over 100.0 due to rounding.

The protocol of the Dow Chemical Co (1980d) study of FR-651G was the same as described above for Dow Chemical Co (1980b, 1980c), with minor alterations. Specifically, 15 controls/sex were used (instead of 10/sex); blood samples for hematology were collected from 7 rats/sex/dose (instead of 5) on Day 84; and comprehensive histopathology examinations were limited to the control and high-dose groups. The liver was examined microscopically in all animals; in addition, reproductive organs (ovaries and uterus) of 10 females in the 30-mg/kg-day group were examined.

There were no deaths, signs of systemic toxicity, or treatment-related ocular effects among the rats following pathologic examination in the Dow Chemical Co (1980d) study. The study authors noted that mechanical malfunctions were experienced with the weighing apparatus that affected body weight and food consumption measurements, and reported that the apparent differences between treated and control animals were not attributable to treatment because the differences reflected implausible measurements (e.g., a 136-g weight gain in 2 weeks). It is possible these malfunctions also affected the organ-weight measurements. Decreases in BUN, serum ALT, and serum ALP were seen in both sexes of rat; however, the toxicological significance is uncertain. No treatment-related hematological changes were observed at any dose or in either sex. Urine specific gravity was significantly decreased (<1%) in high-dose males

compared with controls, but there were no other urinalysis findings. Increases in absolute and relative liver weight, observed in both sexes, were not biologically significant (<10%), but the increase in relative liver weight of high-dose females was statistically significant (see Table B-5); however, the mechanical malfunctions with weight measurements (as noted by the study authors) limit the confidence in organ-weight measurements. Significant histopathology findings were restricted to the liver, and consisted of statistically significant hepatocellular swelling and decreased staining intensity in the centrilobular or central and mid-zonal portions of the liver in 10/10 high-dose males and a statistically nonsignificant increase (3/10) in high-dose females (see Table B-5). One high-dose male also exhibited very slight focal hepatocellular necrosis and inflammation. None of the other organs showed dose-related effects. Based on the liver lesions, a LOAEL of 100 mg/kg-day is identified for this study; the NOAEL is 30 mg/kg-day. The effect levels in this study are uncertain because mechanical problems affecting food consumption and body-weight measurements were reported, rendering the doses estimated by the study authors uncertain.

Dow Chemical Co (1980a)

Dow Chemical Co (1980a) exposed groups of 10 CDF F344 rats/sex (15/sex controls) to FR-651 "slurry dried" in the diet for 92 days. Due to an error in preparation of the premix used in the study (discovered after the study was completed), dietary concentrations during the last month of the study were approximately twice the levels used in the first 2 months. The study authors estimated time-weighted average (TWA) doses of 0, 90, 260, or 780 mg/kg-day FR-651 for 92 days. In the available copy of the report, the composition of the test material was redacted; a handwritten sheet in the Dow Chemical Co (1975) Toxic Substances Control Act (TSCA) submission indicated the FR-651 "slurry dried" composition shown in Table 7.

Table 7. Composition of FR-651 "Slurry Dried"

Compound	Percent Composition
Pentabromochlorocyclohexane	70.7
Tetrabromodichlorocyclohexane	24.2
Tribromotrichlorocyclohexane	5.1
Dibromotetrachlorocyclohexane	0

The Dow Chemical Co (1980a) study of FR-651 "slurry dried" was conducted under the same protocol as (Dow Chemical Co, 1980b, c), with minor alterations. Specifically, 15 controls/sex were used (instead of 10/sex); blood samples for hematology were collected from 7 rats/sex/dose (instead of 5) on Day 84; and comprehensive histopathology examinations were limited to the controls (10/sex) and high-dose groups. The liver, kidneys, and brain were examined microscopically in all animals.

No rats died, and no signs of toxicity were noted (Dow Chemical Co, 1980a). Statistically significantly decreased terminal body weight (see Table B-6) was seen in high-dose males and females (17 and 8% less than controls, respectively). Decreased food consumption was also reported in males (but not females) at this dose during the final month of the study when test material concentrations were doubled (see Table B-6). The study authors noted

"recurrent" mechanical problems with the weighing apparatus. While the authors' discussion pertained to food consumption values, it is possible other weight measures (body and organ weights) were also affected by the malfunctions. Serum chemistry parameters (ALT, BUN, and ALP) were decreased in treated males and females (see Table B-6), but the toxicological significance of these declines is uncertain. Significant hematology findings consisted of increased Hct and Hb in high-dose males only (increases were 3 and 6%, respectively, compared with controls). However, the study authors noted that the Hct value was skewed by an aberrant value in a single animal, and the Hb values were within the normal range for this strain of rat. Urinalysis findings were unremarkable. Relative liver weights were increased (≥10%) in all male treatment groups and in females exposed to 260 or 780 mg/kg-day; absolute liver weights were increased (>10%) in males exposed to 260 mg/kg-day and in females exposed to 260 or 780 mg/kg-day (see Table B-6). Other organ-weight changes, including increased relative (but not absolute) kidney weights and decreased absolute brain and heart weights (data not shown), were attributed to lower fasted body weights in the affected dose groups. All animals of the 260- and 780-mg/kg-day dose groups exhibited liver changes consisting of very slight or slight-to-moderate hepatocellular hypertrophy and altered appearance and staining intensity in the central and mid-zonal areas of the cytoplasm (homogenous eosinophilia) is evident in males dosed with 780 mg/kg-day (see incidences in Table B-6). A LOAEL of 260 mg/kg-day is identified based on liver histopathology in males and females; the NOAEL is 90 mg/kg-day. Statistically significant increases were observed in relative, but not absolute, liver weight in males at all doses. As with the other subchronic-duration studies conducted by this laboratory, the effect levels in this study are uncertain due to mechanical problems affecting food consumption measurements, thus rendering the doses estimated by the authors uncertain.

Chronic-Duration Studies

Dow Chemical Co (1983a, 1983b)

In the study by (Dow Chemical Co, 1983a, b), FR-651A was administered in the diet to groups of 50 male and 50 female F344 rats for 2 years. Dietary concentrations were formulated to yield daily doses of 0, 1, 15, or 50 mg/kg-day FR-651A in males and 0, 1, 20, or, 70 mg/kg-day FR-651A in females. Stability tests indicated that the material was stable in the dietary mixture for up to 30 days. The test material exhibited the composition shown in Table 8.

Table 8. Analysis of FR-651A in 2-year Study by Dow Chemical Co (1983a)

Compound	Percent Composition
Pentabromochlorocyclohexane	76.5
Tetrabromodichlorocyclohexane	19.5
Tribromotrichlorocyclohexane	4.0
Dibromotetrachlorocyclohexane	–

Control groups consisted of 86 male and 86 female rats receiving untreated diets. Additional groups of 15 rats/sex were treated with 0 or 15 mg/kg-day (males) or 0 or 20 mg/kg-day (females) and sacrificed (three/sex) on study Days 10, 30, 45, 90, and 540 for analysis of bromine levels in serum and in adipose and liver tissue. In addition, satellite groups

of 10 rats/sex were administered all doses and sacrificed at 1 year for interim evaluations and histopathology.

All animals were observed twice per week during the first year and daily during the second year for clinical signs of toxicity. Body weights and food consumption were measured weekly for the first 3 months on 20 rats/sex/dose (for use in dietary concentration adjustments to meet target doses) and monthly for all animals (Dow Chemical Co, 1983a, b). Blood samples for hematology (Hct, Hb, RBC count, and total and differential WBC count) and serum chemistry (BUN, ALP, and ALT) were collected from 10 rats/sex/dose prior to euthanasia in both the interim (high-dose and control groups only) and terminal (all dose groups, including 18−20 rats/sex/dose for clinical chemistry) sacrifices. Urine samples were collected from the same groups and analyzed for specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood, and urobilinogen. All animals received gross necropsy at death or scheduled sacrifice. The following organs were weighed: liver, kidneys, brain, heart, and testes. At interim sacrifice, a comprehensive histopathology examination was performed on all rats of the control and high-dose groups. Examination for gross lesions and histopathological examination of the liver were also performed on the low-dose group. At terminal sacrifice, all remaining rats received histology examination of the oral cavity, tongue, esophagus, stomach, small and large intestines, and cecum; the study authors indicated that these tissues were selected based on gross necropsy findings.

Survival to the 2-year study termination was similar in both the control and treated groups of rats (Dow Chemical Co, 1983a, b). In addition, clinical observations did not indicate any differences between treated and control rats. Statistically significant decreases in body weight were observed consistently in male rats exposed to 50 mg/kg-day FR-651A from Day 533 to study termination and in female rats exposed to 70 mg/kg-day during the final 3 months of the study; these decreases were not accompanied by reductions in food consumption. Terminal body weights in high-dose males and females were statistically significantly lower than controls, but the decrements compared with controls were <10% (see Table B-7). No body-weight changes attributable to treatment were observed in the lower dose groups. Statistically significant serum chemistry changes (data not shown) were not dose related and not considered to be related to treatment. Hematology analyses at both the interim and terminal sacrifices showed significant increases in total WBC in males receiving 50 mg/kg-day, but the differential counts did not suggest alterations in the proportions of neutrophils or lymphocytes. There were no statistically significant hematology changes in females (data not shown in Table B-7).

Selected organ weights are shown in Table B-7. At the interim sacrifice, absolute liver weights were statistically significantly increased (≥10% higher than controls) in the male rats receiving 15 or 50 mg/kg-day; relative liver weight was increased only at the high dose (11%). Relative liver weight was statistically significantly increased (7–8%) over controls in females receiving 20 or 70 mg/kg-day at the interim sacrifice, but absolute liver weight was not significantly different from controls (Dow Chemical Co, 1983a, b). Relative liver weight changes in the high-dose groups may have been impacted by decreases in body weight in both males and females in these groups. There were no significant differences in liver weight among the exposed and control groups at the terminal sacrifice. At the interim sacrifice, histopathology findings consisted of "very slight" altered tinctorial (staining) properties and "very slight," multifocal hepatocellular hypertrophy in high-dose males (see Table B-8), and "slightly" increased severity of age-related chronic progressive glomerulonephropathy (incidence not

reported) in high-dose males and females. At terminal sacrifice, the incidences of lesions (dilatation, hypercellularity, and aggregates of cellular debris) in intestinal crypts of the colon were significantly ($p < 0.05$) increased in high-dose males (8/49 vs. 0/84 controls) and females (11/50 vs. 1/86 controls), as shown in Table B-8. A LOAEL of 50 mg/kg-day in male rats is identified based on liver and kidney histopathology at the 1-year interim sacrifice and lesions of the large intestine at termination. The NOAEL is 15 mg/kg-day. The lack of histopathology examination of the liver at the terminal sacrifice is an important limitation of this study.

The incidences of primary polypoid adenoma and/or adenocarcinoma of the colon (see Table B-9) were statistically significantly higher in high-dose animals (5/49 males and 9/50 females) compared with controls (1/84 males and 1/86 females) (Dow Chemical Co, 1983a, b). The tumor incidences were not different from controls at lower doses. As noted above, histopathology examination at termination was restricted to the gastrointestinal tract, limiting the confidence in the carcinogenicity information from this study.

Keyes et al. (1982) as reported in U.S. EPA (1985)

U.S. EPA (1985) summarized the results of a chronic-duration dietary study of FR-651C conducted by Keyes et al. (1982). The primary study report was not available for review. Available information included the study protocol (Dow Chemical Co, 1977), a letter reporting the preliminary results (Dow Chemical Co, 1981), and a summary of the study reported by U.S. EPA (1985). The composition of the test material was not characterized in any of the available literature. FR-651C was administered for 2 years to groups of 50/sex F344 rats in the diet at concentrations intended to yield doses of 1, 15, or 50 mg/kg-day FR-651C in males and 1, 20, or 70 mg/kg-day FR-651C in females; groups of 86 rats/sex served as controls [Keyes et al. (1982) as reported in U.S. EPA (1985)]. In addition, satellite groups of 10 rats/sex were administered all doses and sacrificed at 1 year for interim evaluations and histopathology. All rats were subjected to necropsy and comprehensive histopathology examination at the end of 2 years. According to U.S. EPA (1985), there was no difference in survival between controls and treated animals. The results provided by U.S. EPA (1985) are considered to represent the final results, as the document cited a more recent report than Dow Chemical Co (1981). The only treatment-related finding reported by U.S. EPA (1985) was a significant increase in the incidence of polypoid adenomas of the large intestine in female rats exposed to 70 mg/kg-day; 8/50 females exhibited these tumors, compared with 2/85 controls (see Table B-10). One additional female exhibited a polypoid adenocarcinoma. The tumor incidence in treated male groups was not significantly different from controls. A NOAEL and LOAEL cannot be determined from this study due to the lack of data on non-neoplastic endpoints.

Inhalation Exposures

No studies examining effects of PBCC in animals exposed via inhalation have been identified.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

The genotoxicity database for PBCC is limited to a single study discussed below. Table 9 provides an overview of other supporting studies on PBCC, which include an acute oral lethality study, skin and eye irritation tests, and a skin sensitization test. No studies of PBCC metabolism, toxicokinetics, mechanism, or mode of action have been identified. Data on bromine levels in the tissues of animals exposed to mixtures containing PBCC are discussed below.

Genotoxicity

A single study examining the genotoxicity of PBCC (purity not reported) was identified in the available literature. Zeiger et al. (1992) reported inconclusive results for this compound in Ames assays using *Salmonella typhimurium* strains TA100, TA1535, TA97, and TA98, both with and without metabolic activation. The tests were hampered by precipitation of the test material; precipitates were evident at doses ≥100 µg/plate (doses up to 10,000 µg/plate PBCC were tested). Results at lower doses were negative.

Acute Toxicity Studies

The acute oral lethality of FR-651P (composition not reported) administered via a single gavage dose was estimated to be >5,000 mg/kg FR-651P in male F344 rats and >2,500 mg/kg FR-651P in female F344 rats (Dow Chemical Co, 1986). In the Dow Chemical Co (1958) study, investigators dosed two rats (strain and sex not specified) with 2,000 mg/kg PBCC (specific mixture not reported) by gavage. No mortality (0/2) was observed and the authors reported that PBCC caused no skin or eye irritation. The Dow Chemical Co (1973) study indicated that the acute oral lethality of PBCC (identified as Japanese-produced SE-651) was low, but provided no supporting information. Likewise, Dow Chemical Co (1975) reported that the LD_{50} in rats was >2 g/kg for a sample characterized only as pentabromochlorocyclohexane; no further details were given.

Dow Chemical Co (1959a, 1959b) reported anecdotally that plant personnel handling SE-651 had experienced eye irritation or "general eye discomfort" and corneal burns; these findings led to animal testing for skin and eye irritation. No information on exposure conditions in the plant(s), or other supporting information, was provided. Tests of SE-651 for eye irritation in the rabbit were equivocal. Dow Chemical Co (1959b) observed that a saturated solution of SE-651 appeared "discomforting," but concluded that the test material was essentially nonirritating. Dow Chemical Co (1964) applied several different samples of undiluted SE-651 to rabbit eyes and observed slight conjunctival redness that cleared within 24 hours, and concluded that the test material may be slightly irritating to the eyes.

Skin irritation tests using SE-651 (also described as FR-651) applied to intact or abraded skin of rabbits indicated that SE-651 was slightly irritating in a saturated solution in Dowanol DPM (dipropylene glycol methyl ether), but not irritating in undiluted form (Dow Chemical Co, 1979c, d, 1959b). Dow Chemical Co (1973) reported that regular contact of Japanese-produced SE-651 with skin would likely induce slight erythema, but the study authors provided no supporting information.

Dow Chemical Co (1979c, 1979d) reported that SE-651 (also described as FR-651) was a potential skin sensitizer based on erythema seen in male guinea pigs treated with SE-651 in Dowanol DPM: Tween 80 (9:1); however, other details of the methods used were not reported.

Table 9. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Human studies				
ND				
Animal toxicity studies				
Acute studies	FR-651P (composition not reported) administered as a 25% suspension in corn oil via single gavage dose to three male and three female F344 rats. Mortality, clinical signs, and body weights were monitored during a 14-d post-treatment observation period.	0/3 male rats died at 5,000 mg/kg; 0/3 female rats died at 2,500 mg/kg. Clinical signs were limited to diarrhea. One male rat was lethargic with palpebral closure.	Oral LD_{50} of FR-651P may be >5,000 mg/kg in male rats and >2,500 mg/kg in female rats; limited basis to draw conclusion.	Dow Chemical Co (1986)
Acute studies	Test material, characterized as pentabromochlorocyclohexane, was administered orally as 10% solution in corn oil to two rats.	0/2 rats died at 2,000 mg/kg. Liver damage (no further details) was observed at autopsy.	Inadequate information to draw a conclusion.	Dow Chemical Co (1958)
Acute studies	A single dose of test material, characterized as PBCC, was administered orally in corn oil to rats by gavage. PBCC was also applied to the eyes and skin of rabbits.	No mortality at the highest dose (2,000 mg/kg); slight effect on kidneys (pale color and edematous). PBCC may be slightly irritating to eyes; no evidence of skin irritation.	Oral LD_{50} may be >2,000 mg/kg. PBCC may be slightly irritating to the eyes. PBCC not irritating to rabbit skin but may be irritating to humans after prolonged contact.	Dow Chemical Co (1975, 1958)
Acute studies other than oral/inhalation	SE-651 applied to rabbit eye as powder or as saturated solution in propylene glycol.	The study authors reported that saturated solution appeared “discomforting” but conjunctivae and corneas were undisturbed.	SE-651 in solution is not considered an eye irritant.	Dow Chemical Co (1959b)
Acute studies other than oral/inhalation	Several different samples of undiluted SE-651 applied to rabbit eyes.	Very slight to slight conjunctival redness observed; eyes cleared in 24 hr.	Undiluted SE-651 may be slightly irritating to the eyes.	Dow Chemical Co (1964)

Table 9. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute studies other than oral/inhalation	"Fire retardant for styrofoam" (80% PBCC with other ingredients) applied daily for 3 or 10 d to intact and abraded skin of rabbits (ear or belly), undiluted or as saturated solution in Dowanol DPM.	When applied undiluted, no irritation occurred. When applied in solution to either intact or abraded skin, slight hyperemia and slight exfoliation observed; skin normal at 14 d.	Test material in undiluted form is considered nonirritating to skin; in solution, it is slightly irritating to skin.	Dow Chemical Co (1959b)
Acute studies other than oral/inhalation	Several different samples of wetted SE-651 applied daily for 3 or 10 d to intact and abraded skin of rabbits (ear or belly), undiluted.	No sample produced more than slight irritation to intact skin, observed as redness, exfoliation, and occasional swelling. Repeated exposure of abraded skin to some samples resulted in slight skin burns.	SE-651 is slightly irritating to intact skin, and may cause burns to abraded skin.	Dow Chemical Co (1964)
Acute studies other than oral/inhalation	SE-651 (Japanese-produced, 85.3% PBCC) tested for eye and skin irritation; methodological details not reported.	Test material characterized as essentially nonirritant to eye, and regular contact with skin likely to induce slight erythema. No details provided.	Inadequate information to draw a conclusion.	Dow Chemical Co (1973)
Acute studies other than oral/inhalation	FR-651 applied repeatedly to skin of male New Zealand albino rabbits. No further details of methods provided.	Authors reported no perceptible primary irritation.	FR-651 is not considered a skin irritant.	Dow Chemical Co (1979c, 1979d)
Acute studies other than oral/inhalation	FR-651 applied as 10% solution in Dowanol DPM: Tween 80 (9:1) to skin of 10 male Hartley guinea pigs to test skin sensitization. No further details of methods provided.	Authors reported very slight to moderate redness in 8/10 guinea pigs. No further details were provided.	FR-651 is considered a potential skin sensitizer.	Dow Chemical Co (1979c, 1979d)

ND = no data

Metabolism/Toxicokinetic Studies

No studies examining the toxicokinetic behavior of PBCC in humans or animals have been identified.

In the subchronic-duration studies of FR-651A, FR-651G, and FR-651 "slurry dried" described above (Dow Chemical Co, 1980a, b, c), bromine content of the adipose tissue, liver, and kidney of treated and control rats was measured at termination. In all three studies, increased bromine levels were detected in treated animals relative to controls. Bromine concentrations were higher in the kidney than liver or adipose (kidney > liver > adipose tissue). Concentrations increased across dose groups in a dose-related manner. No sex differences in bromine concentrations were evident. The authors estimated that about 1–2% of the total bromine ingested was in these tissues at termination (Dow Chemical Co, 1980a, b, c).

In the chronic-duration toxicity study of FR-651A described above (Dow Chemical Co, 1983a, b), groups of three/sex of the control and mid-dose rats (15 mg/kg-day FR-651A in males and 20 mg/kg-day FR-651A in females) were sacrificed for measurement of bromine in the adipose tissue, liver, and serum on Days 10, 30, 45, 90, 365, 540, and 734 of the study. Bromine content in control and high-dose animal tissues was measured at the interim (1 year) and terminal sacrifices. Increased bromine levels were detected in treated animals (relative to controls) at every time point. The highest concentrations of bromine were in the serum (serum > liver > adipose tissue); bromine content of the kidneys was not analyzed in this study. Table 10 provides information on the bromine concentrations after 10 and 734 days of exposure to FR-651A. As the table shows, concentrations in these tissues increased over the 2-year study period, reaching final concentrations slightly more than twofold higher than the concentrations at Day 10 of the study.

Table 10. Bromine Concentration in F344 Rats Exposed to FR-651A in the Diet for 2 Years[a]

	Mean Concentration of Bromine (ppm)			
	Males		Females	
Tissue (days)	**10**	**734**	**10**	**734**
Serum	93	242	111	276
Liver	31	73	38	74
Adipose	12	24	17	33

[a]Dow Chemical Co (1983a, 1983b).

DERIVATION OF PROVISIONAL VALUES

Tables 11 and 12 present summaries of noncancer and cancer reference values, respectively.

Table 11. Summary of Noncancer Screening Reference Values for PBCC (CASRN 87-84-3)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value[a]	POD Method	POD[a]	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-d)	Rat (strain not specified)/females	Elevated liver weight; centrilobular degeneration and necrosis	2×10^{-2} (as SE-651)	NOAEL	30 HED: 7.3	300	Dow Chemical Co (1960)
Screening chronic p-RfD (mg/kg-d)	F344 rat/males	Portal-of-entry effect: Intestinal lesions (dilatation, hyper-cellularity, and aggregates of cellular debris)	2×10^{-2} (as FR-651A)	$BMDL_{10}$	20	1,000	Dow Chemical Co (1983a, 1983b)
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

[a]Portal-of-entry effects not converted to HED.

$BMDL_{10}$ = 10% benchmark dose lower confidence limit; HED = human equivalent dose; NDr = not determined; NOAEL = no-observed-adverse-effect level; p-RfC = provisional reference concentration; p-RfD = provisional reference dose.

Table 12. Summary of Cancer Screening Reference Values for PBCC (CASRN 87-84-3)

Toxicity Type (units)	Species/Sex	Tumor Type	Cancer Value[a]	Principal Study
Screening p-OSF $(mg/kg\text{-}d)^{-1}$	Rat/females	Portal-of-entry effect: Polypoid adenomas and adenocarcinomas of the large intestine	2×10^{-2} (as FR-651A)	Dow Chemical Co (1983a, 1983b)
p-IUR $(mg/m^3)^{-1}$	NDr			

[a]Portal-of-entry effects not converted to HED.

NDr = not determined; p-IUR = provisional inhalation unit risk; p-OSF = provisional oral slope factor.

DERIVATION OF ORAL REFERENCE DOSES

There are no in vivo toxicological data on pure PBCC. Information on the oral toxicity of PBCC is available from several unpublished studies of commercial mixtures containing this compound. These include two 29-day experiments in rats (TRL, 1987; Dow Chemical Co, 1979a, b), four subchronic-duration (90–92 day) experiments in rats (Dow Chemical Co, 1990, 1980a, b, c, d, 1960), and two 2-year chronic-duration toxicity and carcinogenicity studies in rats [Keyes et al. (1982) as cited in U.S. EPA (1985); Dow Chemical Co (1983a, 1983b)].

The available information is not considered sufficiently reliable for use in deriving provisional subchronic and chronic reference doses (p-RfDs) for several reasons. First, the

studies tested mixtures containing between 50.3 and 85.3% PBCC with variable concentrations of other congeners (see Table 3). Second, the available studies were unpublished and conducted by the same laboratory, the Dow Chemical Co., using the same species (rat) and strain (F344). Third, three of the four subchronic-duration studies (Dow Chemical Co, 1980a, b, c) reported mechanical problems with the weighing apparatus, which the study authors indicated could have affected food consumption measurements (and in one case, body-weight measurements). Thus, the doses and body weights estimated by the authors are uncertain. Fourth, two chronic-duration studies are available, but the primary report for the chronic-duration study of FR-651C mixture is not available for review, and the chronic-duration study of the FR-651A mixture did not include a comprehensive histopathology examination at termination. Importantly, the tissues examined microscopically at termination in the study of FR-651A did not include the liver, which was identified as a primary target tissue in all of the short-term-, subchronic- and chronic-duration studies (Dow Chemical Co, 1990, 1983a, b, 1980a, b, c, d, 1979a, b, 1960) of the various formulations and at the interim sacrifice of the chronic-duration study of FR-651A. Although the liver weights of PBCC-treated rats were statistically ($p < 0.05$) and biologically significantly elevated (10−13% at the two highest doses) at the 1-year interim sacrifice, the rat liver weights were not statistically or biologically significantly elevated at the 2-year termination. Because the liverweight increases appeared to resolve over time, they are not considered further as a potential point of departure (POD) for chronic-duration exposures.

Due to the uncertainties in the available data for PBCC, subchronic and chronic p-RfDs were not derived. Instead, screening subchronic and chronic p-RfDs are derived in Appendix A.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No studies of humans or animals exposed to PBCC (alone or as a mixture) via inhalation have been identified in the available literature, precluding derivation of provisional inhalation reference concentrations (p-RfCs).

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 13 provides the cancer weight-of-evidence (WOE) descriptor for PBCC. Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), PBCC exhibits *"Suggestive Evidence of Carcinogenic Potential"* based on evidence of carcinogenicity in orally treated male and female rats. This descriptor is based on the occurrence of adenomas and adenocarcinomas of the large intestines in male and female F344 rats at the highest dose (FR-651A) tested in Dow Chemical Co (1983a, 1983b) and also on the occurrence of adenomas and adenocarcinomas of the large intestines in female F344 rats at the highest dose of a related PBCC mixture (FR-651C) [Keyes et al. (1982) as cited in U.S. EPA (1985)].

Table 13. Cancer WOE Descriptor for PBCC			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	There are no data to support this conclusion.
"Likely to Be Carcinogenic to Humans"	NS	NA	There are no suitable animal studies to support this conclusion. Tumors observed in only one strain (F344) of one species (rat), in only one organ, and a dose response was not demonstrated.
"Suggestive Evidence of Carcinogenic Potential"	**Selected**	**Oral**	**Two chronic-duration studies of F344 rats orally exposed to mixtures in which PBCC was the primary constituent have shown increased incidences of intestinal tumors [Keyes et al. (1982) as cited in U.S. EPA (1985); Dow Chemical Co (1983a, 1983b)].**
"Inadequate Information to Assess Carcinogenic Potential"	NS	NA	Available studies are sufficient to assess carcinogenic potential.
"Not Likely to Be Carcinogenic to Humans"	NS	NA	There are no suitable animal studies to support this conclusion.

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

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Data on the oral carcinogenicity of PBCC are available in two 2-year carcinogenicity studies of mixtures in rats [Keyes et al. (1982) as cited in U.S. EPA (1985); Dow Chemical Co (1983a, 1983b)]. The available information is not considered sufficiently reliable for use in deriving provisional cancer potency values for several reasons. First, both of the available studies are unpublished and conducted by or for the Dow Chemical Co. Second, the primary report for the carcinogenicity study of FR-651C is not available for review, and the carcinogenicity study of FR-651A did not include comprehensive histopathology examination at termination, based in part on the findings of the study of FR-651C. The tissues examined after 2 years in the study of FR-651A did not include the liver, which was identified as the primary target tissue in subchronic-duration studies of the various formulations and at the 1-year interim sacrifice in the 2-year study of FR-651A (Dow Chemical Co, 1983a, b). The presence of other tumors associated with PBCC exposure cannot be determined in this study because the histopathological examination at the 2-year termination was limited to the gastrointestinal tract.

Due to the uncertainties in the available data for PBCC, provisional cancer potency values were not derived; however, a "screening value" for oral cancer potency of the FR-651A PBCC mixture is provided in Appendix A.

No carcinogenicity studies of humans or animals exposed to PBCC (alone or as a mixture) via inhalation have been identified in the available literature, precluding derivation of inhalation cancer potency values.

APPENDIX A. SCREENING PROVISIONAL VALUES

For the reasons noted in the main document, provisional toxicity values for 1,2,3,4,5-Pentabromo-6-chlorocyclohexane (PBCC) could not be derived. However, information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the main documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a provisional peer-review toxicity value (PPRTV) assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Heath Risk Technical Support Center.

DERIVATION OF SCREENING ORAL REFERENCE DOSES

The screening toxicity values derived in this document apply only to the specific mixtures of PBCC tested in the principal studies (i.e., SE-651 for the screening subchronic provisional reference dose [p-RfD] and FR-651A for the screening chronic p-RfD and screening provisional oral slope factor [p-OSF]). Dose adjustment may be necessary before extrapolating to other mixtures of PBCCs.

The 90-day rat study of PBCC (SE-651) conducted by the Dow Chemical Co (1960) is selected as the principal study for derivation of a screening subchronic p-RfD. Of the four available subchronic-duration studies available (see Table 4A), only the Dow Chemical Co (1960) study did not report malfunctions in the weighing system, which rendered body weights and food consumption estimates unreliable. In the principal study, male and female F344 rats (10/sex/dose) were dosed for 90 days with 0, 10, 30, 100, 300, or 1,000 mg/kg-day (human equivalent doses [HEDs]: 0, 2.4, 7.2, 24.4, 73.3, or 244.5 mg/kg-day). Relative liver and kidney weights were elevated at statistically significant levels in males and females at 300 mg PCBB/kg-day and higher. Histopathological examination confirmed the elevated organ weights seen at higher doses and showed central lobular granular degeneration and necrosis in the liver and interstitial and tubular nephritis of the kidney at 100 mg/kg-day. The organ-weight results were reported as group means without a standard deviation (SD) and the histopathology results were qualitatively described without incidence data. As a result, benchmark dose (BMD) modeling was not possible. A no-observed-adverse-effect level (NOAEL) of 30 mg/kg-day is based on male histopathological liver effects at 100 mg/kg-day which is confirmed by statistically significantly elevated relative liver weight at 300 mg/kg-day in the absence of significant body weight (BW) reduction. Selection of liver alterations as the critical effect is supported by the Dow Chemical Co. that consistently found the liver to be a target organ in short-term-, subchronic-, and chronic-duration exposures to PBCC mixtures.

The NOAEL of 30 mg/kg-day based on liver effects in male rats identified in Dow Chemical Co (1960) is the selected point of departure (POD) for derivation of the screening subchronic p-RfD. In *Recommended Use of Body Weight 3/4 as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), the Agency endorses a hierarchy of

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

A validated human physiologically based toxicokinetic model for PBCC is not available for use in extrapolating doses from animals to humans. Furthermore, the selected liver alterations in male rats are not portal of entry effects. Therefore, scaling by $BW^{3/4}$ is relevant for deriving an HED for these effects.

Following U.S. EPA (2011b) guidance, the POD (30 mg/kg-day) from the Dow Chemical Co (1960) study is converted to an HED through the application of a dosimetric adjustment factor (DAF)[1] derived as follows:

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

where

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

Using a reference BW_a of 0.25 kg for rats and a reference BW_h of 70 kg for humans (U.S. EPA, 1988), the resulting DAF is 0.24. Applying this DAF to the POD identified in the Dow Chemical Co (1960) study yields a POD (HED) as follows:

$$\begin{aligned} \text{POD (HED)} &= \text{NOAEL (mg/kg-day)} \times \text{DAF} \\ &= \text{NOAEL (mg/kg-day)} \times 0.24 = 30 \text{ mg/kg-day} \times 0.24 \\ &= 7.2 \text{ mg/kg-day} \end{aligned}$$

The screening subchronic p-RfD for PBCC (SE-651) is derived as follows:

$$\begin{aligned} \textbf{Screening Subchronic p-RfD} &= \text{POD (HED)} \div UF_C \\ &= 7.2 \text{ mg/kg-day} \div 300 \\ &= \mathbf{2 \times 10^{-2} \text{ mg/kg-day}} \end{aligned}$$

Table A-1 summarizes the uncertainty factors for the screening subchronic p-RfD for mixtures containing PBCC described in this PPRTV document.

[1]As described in detail in *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b), rate related processes scale across species in a manner related to both the direct ($BW^{1/1}$) and allometric scaling ($BW^{3/4}$) aspects such that $BW^{3/4} \div BW^{1/1} = BW^{-1/4}$, converted to a $DAF = BW_a^{1/4} \div BW_h^{1/4}$.

Table A-1. Uncertainty Factors for the Screening Subchronic p-RfD for Mixtures Containing PBCC

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicokinetic or toxicodynamic differences between rats and humans following PBCC exposure. The toxicokinetic uncertainty has been accounted for by calculation of an HED through application of a DAF as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b).
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of PBCC in humans.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database, specifically the lack of data on reproductive or developmental toxicity and the lack of data in a second species.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL, not a LOAEL.
UF_S	1	A UF_S of 1 is applied because the POD comes from a subchronic-duration study of rats.
UF_C	300	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

DAF = dosimetric adjustment factor; HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor.

Derivation of a Screening Chronic Provisional Reference Dose

The 2-year rat study of PBCC (FR-651A) conducted by Dow Chemical Co (1983a, 1983b) is selected as the principal study for derivation of a screening chronic p-RfD. The principal study dosed male and female F344 rats (50/sex/dose) with controls of 86 rats/sex for 2 years with one of four doses: 0, 1, 15, or 50 mg/kg-day in males and 0, 1, 20, or 70 mg/kg-day in females. HEDs for systemic effects are 0, 0.2, 3.7, or 12.2 mg/kg-day in males and 0, 0.2, 4.9, or 17.1 mg/kg-day in females. As shown in Table 4A, the lowest-observed-adverse-effect level (LOAEL) of the available studies (50 mg/kg-day in males and 70 mg/kg-day in females) is identified in the Dow Chemical Co (1983a, 1983b) chronic-duration study of PBCC (FR-651A). In addition, FR-651A contains the highest proportion of PBCC (77%) among the mixtures with toxicological data (see Table 3); thus, it provides the best data for screening levels for PBCC. Finally, no mechanical problems with weight measurements were reported in the chronic-duration study (Dow Chemical Co, 1983a, b).

Effects seen at the LOAEL in the Dow Chemical Co (1983a, 1983b) included (1) increased absolute and/or relative liver weight in males and females at the interim (but not terminal) sacrifice; (2) increased incidences of hepatocellular hypertrophy and altered tinctorial (staining) properties of hepatocytes in males at the interim sacrifice; (3) increased severity of age-related chronic progressive glomerulonephropathy in males and females at the interim sacrifice; and (4) lesions of the large intestine at termination. The incidence of histopathology findings in the large intestines of male and female rats is selected for BMD modeling to identify a POD for screening chronic p-RfD derivation. Liver-weight measures are not considered for use in deriving the screening chronic p-RfD because the liver-weight changes seen at the interim sacrifice were no longer apparent at the terminal sacrifice.

Liver histopathology endpoints observed at the interim sacrifice were considered as a potential POD because the liver is a target organ in all of the studies conducted by the Dow Chemical Co. [Dow Chemical Co (1990, 1983a, 1983b, 1980a, 1980b, 1980c, 1980d, 1979a, 1979b, 1960); Keyes et al. (1982) as cited in U.S. EPA (1985)]. The histopathological examination (Dow Chemical Co, 1983a, b) reported 34 non-neoplastic liver parameters at the 1-year interim sacrifice (10 rats/sex/dose). Only two parameters, altered multifocal hepatocellular tinctorial (staining) properties (9/10) and multifocal hepatocellular hypertrophy (9/10), demonstrated a statistically significant ($p < 0.05$) dose-related increase above the control rats. Both effects were observed only in males (0/10 in females) and only at the highest dose (50 mg/kg-day). These effects were not observed at lower doses or in the control animals (0/10). The severity of both effects was reported in the study as "very slight." The severity of the remaining 32 liver parameters was reported to be "slight" or "very slight," and none demonstrated a statistically significant dose-related trend. The study authors did not conduct a histopathological exam of the liver at the 2-year terminal sacrifice, but they did conduct a gross pathological exam of major organ systems and tissues. In the livers, pathologists looked at 22 parameters and reported no dose-related changes. Because of the low severity and the uncertain toxicological significance of the liver effects reported at the interim histopathological exam, coupled with the lack of evidence for liver damage in the gross pathological exam, the liver was not considered suitable as a target organ for deriving a screening chronic p-RfD. Finally, the incidences of age-related chronic progressive glomerulonephropathy were not reported, so this endpoint is not considered as the basis for screening p-RfD derivation.

As described in Appendix C, BMD modeling was performed on the incidence of dilation, hypercellularity, and aggregates of cellular debris in intestinal crypts in male and female rats in the principal study (Dow Chemical Co, 1983a, b). The lower benchmark dose lower confidence limit 10% ($BMDL_{10}$) of 20 mg/kg-day in males was selected as the POD for chronic p-RfD derivation. The liver histopathology effects (hepatocellular hypertrophy and altered staining properties of hepatocytes) and intestinal lesions were reported at the same LOAEL (50 mg/kg-day) in the principal study (Dow Chemical Co, 1983a, b); therefore, it is presumed that the ($BMDL_{10}$) of 20 mg/kg-day for histopathological findings in the large intestines is also protective against any potential liver effects.

The critical effect for the screening chronic p-RfD (intestinal lesions) may represent a portal-of-entry effect. Because available dosimetric scaling approaches may not be appropriate for portal-of-entry effects, a dosimetric adjustment of the POD to an HED was not used (U.S. EPA, 2011b); instead, the default interspecies UF_A of 10 was used to extrapolate from the POD in animals to the POD in humans.

The screening chronic p-RfD for FR-651A is derived as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= \text{POD} \div UF_C \\ &= BMDL_{10} \div UF_C \\ &= 20 \text{ mg/kg-day} \div 1{,}000 \\ &= \mathbf{2 \times 10^{-2} \text{ mg/kg-day}} \end{aligned}$$

Table A-2 summarizes the uncertainty factors for the screening chronic p-RfD for mixtures containing PBCC described in this PPRTV document.

Table A-2. Uncertainty Factors for the Screening Chronic p-RfD for Mixtures Containing PBCC

UF	Value	Justification
UF_A	10	A UF_A of 10 is applied to account for uncertainty associated with extrapolating from animals to humans in the absence of data with which to perform interspecies dose scaling.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of PBCC in humans.
UF_D	10	A UF_D of 10 is applied to account for deficiencies and uncertainties in the database, specifically the lack of data on reproductive or developmental toxicity and the lack of data in a second species.
UF_L	1	A UF_L of 1 is applied because the POD is a BMDL, not a LOAEL.
UF_S	1	A UF_S of 1 is applied because the POD comes from a chronic-duration study of rats.
UF_C	1,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$.

BMDL = benchmark dose lower confidence limite; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor.

DERIVATION OF SCREENING PROVISIONAL CANCER POTENCY VALUES

Two studies examined the carcinogenic potential of mixtures containing PBCC administered orally to rats for 2 years [Keyes et al. (1982) as cited in U.S. EPA (1985); Dow Chemical Co (1983a, 1983b)]. A detailed report of the design and results was available only for the Dow Chemical Co (1983a, 1983b) study of FR-651A; results of the Keyes et al. (1982) as cited in U.S. EPA (1985) study of FR-651C were obtained from secondary sources (U.S. EPA, 1985; Dow Chemical Co, 1981). Both studies used the same doses, and the tumor types seen in both studies were the same (polypoid adenomas and adenocarcinomas of the intestines). Statistically significant increases in incidence (in pairwise comparisons) were seen in males and females exposed to FR-651A and in females exposed to FR-651C. According to information provided by U.S. EPA (1985), incidences of tumors in females exposed to FR-651C were slightly lower than the incidences in females exposed to FR-651A at the same doses (see Tables B-9 and B-10). For this reason and because the full results were only available from the Dow Chemical Co (1983a, 1983b) study, the cancer data from study of FR-651A were subjected to BMD modeling, but data from the study of FR-651C were not. Furthermore, confidence in the principal study is limited because organs and tissues outside of the gastrointestinal (GI) tract were not examined histopathologically at the terminal sacrifice.

Derivation of a Screening p-OSF

The screening p-OSF for PBCC is based on the incidences of intestinal tumors in female rats exposed to FR-651A for 2 years (Dow Chemical Co, 1983a, b) and was derived as follows:

Prior to dose-response modeling, doses administered in the study by Dow Chemical Co (1983a, 1983b) were converted to HEDs according to the equation below:

$$\text{Dose (HED)} = \text{Dose} \times (BW_a/BW_h)^{1/4}$$

where:

Dose = average daily animal dose
BW_a = TWA rat body weight in study (Dow Chemical Co, 1983a, b)
BW_h = 70 kg, reference human body weight (U.S. EPA, 1988)

BMD modeling of the data on incidences of polypoid adenomas and adenocarcinomas of the intestines in both male and female rats exposed to FR-651A yielded $BMDL_{10}$ (HED) estimates of 11 and 5.9 mg/kg-day, respectively. The lower $BMDL_{10}$ (HED) of 5.9 mg/kg-day, obtained from data on female rats, was selected as the POD for calculation of the screening p-OSF. Because the Dow Chemical Co (1983a, 1983b) study was conducted for the full lifetime of the rats (2 years), no adjustment for less-than-lifetime observation was necessary.

The **screening p-OSF of 2×10^{-2} (mg/kg-day)$^{-1}$** was derived as follows:

Screening p-OSF = BMR ÷ $BMDL_{10}$ (HED)
= 0.1 ÷ 5.9 mg/kg-day
= **2×10^{-2} (mg/kg-day)$^{-1}$**

The screening p-OSF should not be used with exposure exceeding the POD (5.9 mg/kg-day) because at doses higher than this value, the fitted dose-response model better characterizes the dose-response relationship. Further, the screening p-OSF should not be extrapolated to PBCC mixtures with compositions differing greatly from that of FR-651A because there are no data to support such extrapolation.

APPENDIX B. DATA TABLES

Table B-1. Selected Effects on Male and Female CDF F344 Rats Exposed to FR-651A in Food for 29 Days[a]

Endpoint	Exposure Group (mg/kg-d)					
	0	10	30	100	300	1,000
Males						
Number of animals	5	5	5	5	5	5
BUN (mg/100 mL)	18 ± 2[b]	18 ± 3	17 ± 2	17 ± 2	19 ± 2	17 ± 1
Serum ALT (mU/mL)	59 ± 4	52 ± 6	46 ± 4*	55 ± 11	45 ± 5*	45 ± 3*
Terminal body weight (g)	201 ± 24	194 ± 34 (−3.5%)	204 ± 18 (1.5%)	207 ± 21 (3.0%)	188 ± 22 (−6.5%)	206 ± 14 (2.5%)
Absolute liver weight (g)	6.39 ± 1.00	5.85 ± 0.88 (−8.5%)	6.61 ± 0.85 (3.4%)	7.02 ± 0.85 (9.9%)	6.37 ± 0.91 (−0.3%)	7.74 ± 0.36* (21.1%)
Relative liver weight (g/100 g)	3.16 ± 0.13	3.03 ± 0.13 (−4.1%)	3.23 ± 0.18 (2.2%)	3.39 ± 0.11* (7.3%)	3.38 ± 0.17 (7.0%)	3.77 ± 0.19* (19.3%)
Absolute kidney weight (g)	1.60 ± 0.18	1.47 ± 0.21 (−8.1%)	1.62 ± 0.13 (1.3%)	1.63 ± 0.11 (1.9%)	1.52 ± 0.12 (−5.0%)	1.57 ± 0.12 (−1.9%)
Relative kidney weight (g/100 g)	0.79 ± 0.01	0.76 ± 0.04 (−3.8%)	0.79 ± 0.01 (0%)	0.79 ± 0.04 (0%)	0.81 ± 0.04 (2.5%)	0.76 ± 0.06 (−3.8%)
Females						
Number of animals	5	5	5	5	5	5
BUN (mg/100 mL)	21 ± 4	18 ± 1	18 ± 2	17 ± 1	18 ± 4	16 ± 3*
Serum ALT (mU/mL)	49 ± 4	40 ± 2*	42 ± 6	49 ± 6	41 ± 3	45 ± 4
Terminal body weight (g)	124 ± 8	129 ± 8 (4.0%)	133 ± 11 (7.3%)	133 ± 3 (7.3%)	129 ± 13 (4.0%)	140 ± 4* (12.9%)
Absolute liver weight (g)	3.61 ± 0.35	3.77 ± 0.17 (4.4%)	4.11 ± 0.37 (13.9%)	3.96 ± 0.09 (9.7%)	4.01 ± 0.49 (11.1%)	4.54 ± 0.13* (25.8%)
Relative liver weight (g/100 g)	2.91 ± 0.17	2.92 ± 0.14 (0.3%)	3.09 ± 0.07 (6.2%)	2.99 ± 0.10 (2.7%)	3.11 ± 0.13 (6.9%)	3.24 ± 0.09* (11.3%)
Absolute kidney weight (g)	1.0 ± 0.08	1.03 ± 0.04 (3.0%)	1.08 ± 0.10 (8.0%)	1.10 ± 0.04 (10.0%)	1.05 ± 0.12 (5.0%)	1.17 ± 0.04* (17.0%)
Relative kidney weight (g/100 g)	0.80 ± 0.03	0.80 ± 0.03 (0%)	0.81 ± 0.04 (1.3%)	0.83 ± 0.02 (3.7%)	0.81 ± 0.02 (1.3%)	0.83 ± 0.01 (3.7%)

[a]Dow Chemical Co (1979b); TRL (1987).
[b]Mean ± standard deviation.
*Significantly different from control using Dunnett's test ($p < 0.05$), as reported by study authors.

Table B-2. Selected Effects on Male and Female CDF F344 Rats Exposed to FR-651G in Food for 29 Days[a]

Endpoint	Exposure Group (mg/kg-d)					
	0	10	30	100	300	1,000
Males						
Number of animals per group	5	5	5	5	5	5
Final body weight (g)	243 ± 23[b]	223 ± 29 (−8.2%)	221 ± 19 (−9.1%)	239 ± 38 (−1.6%)	227 ± 17 (−6.6%)	193 ± 14* (−20.6%)
BUN (mg/100 mL)	18 ± 1	18 ± 2	18 ± 2	17 ± 2	17 ± 1	17 ± 2
Serum ALT (mU/mL)	53 ± 7	46 ± 4	51 ± 9	45 ± 4	32 ± 1*	36 ± 5*
Serum ALP (mU/mL)	247 ± 25	201 ± 22*	210 ± 24*	217 ± 19	133 ± 13*	208 ± 15*
Absolute liver weight (g)	6.99 ± 0.73	6.31 ± 0.80 (−9.7%)	6.64 ± 0.79 (−5.0%)	7.37 ± 1.46 (5.4%)	9.11 ± 0.68* (30.3%)	8.04 ± 0.89 (15.0%)
Relative liver weight (g/100 g)	3.16 ± 0.16	3.16 ± 0.16 (0%)	3.35 ± 0.15 (6.0%)	3.39 ± 0.27 (7.3%)	4.49 ± 0.11* (42.1%)	4.47 ± 0.14* (41.5%)
Absolute kidney weight (g)	1.68 ± 0.16	1.63 ± 0.22 (7.9%)	1.60 ± 0.18 (6.6%)	1.77 ± 0.26 (7.9%)	1.84 ± 0.15 (19.7%)	1.64 ± 0.16 (21.1%)
Relative kidney weight (g/100 g)	0.76 ± 0.05	0.82 ± 0.03 (7.9%)	0.81 ± 0.03 (6.6%)	0.82 ± 0.02 (7.9%)	0.91 ± 0.01* (19.7%)	0.92 ± 0.05* (21.1%)
Slight darkened appearance of liver	0/5[c]	0/5	0/5	0/5	4/5	5/5
Pale appearance of kidneys						
Equivocal	0/5	0/5	0/5	2/5	0/5	1/5
Slight	0/5	0/5	0/5	0/5	5/5	4/5
Females						
Number of animals per group	5	5	5	5	5	5
Final body weight (g)	140 ± 4	141 ± 16 (0.7%)	141 ± 5 (0.7%)	154 ± 12 (10.0%)	152 ± 11 (8.6%)	137 ± 16 (−2.1%)
BUN (mg/100 mL)	22 ± 2	20 ± 2	17 ± 1*	16 ± 2*	16 ± 1*	15 ± 1*
Serum ALT (mU/mL)	54 ± 12	42 ± 2	41 ± 4	32 ± 13*	40 ± 5	32 ± 6*
Serum ALP (mU/mL)	188 ± 16	190 ± 18	176 ± 26	148 ± 18*	138 ± 15*	117 ± 18*
Absolute liver weight (g)	3.60 ± 0.23	3.78 ± 0.46 (5.0%)	3.96 ± 0.19 (10.0%)	4.49 ± 0.49* (24.7%)	5.12 ± 0.43* (42.2%)	5.49 ± 0.62* (52.5%)
Relative liver weight (g/100 g)	2.91 ± 0.11	3.00 ± 0.09 (3.1%)	3.15 ± 0.11 (8.2%)	3.23 ± 0.14* (11.0%)	3.74 ± 0.22* (28.5%)	4.49 ± 0.23* (54.3%)
Absolute kidney weight (g)	1.00 ± 0.06	1.06 ± 0.12 (9.6%)	1.06 ± 0.04 (6.0%)	1.16 ± 0.12 (16.0%)	1.18 ± 0.10 (18.0%)	1.11 ± 0.16 (11.0%)
Relative kidney weight (g/100 g)	0.81 ± 0.03	0.84 ± 0.03 (3.7%)	0.84 ± 0.02 (3.7%)	0.83 ± 0.02 (2.5%)	0.86 ± 0.04 (6.2%)	0.91 ± 0.04* (12.3%)

Table B-2. Selected Effects on Male and Female CDF F344 Rats Exposed to FR-651G in Food for 29 Days[a]

Endpoint	Exposure Group (mg/kg-d)					
	0	10	30	100	300	1,000
Females						
Darkened appearance of liver						
Equivocal	0/5	0/5	0/5	0/5	2/5	0/5
Slight	0/5	0/5	0/5	1/5	1/5	4/5
Diffuse	0/5	0/5	0/5	0/5	1/5	0/5

[a]Dow Chemical Co (1979a).
[b]Mean ± standard deviation.
[c]Number affected/number examined.
*Significantly different from control using Dunnett's test ($p < 0.05$), as reported by study authors.

Table B-3. Mean Body and Organ Weights of Male and Female Rats[a] Exposed to SE-651 in Food for 90 Days[b]

Endpoint	Dose (mg/kg-d)					
	0	10	30	100	300	1,000
Males						
Number of animals	10	9	10	10	10	10
Average body weight (g)	321	301 (−6.2%)	309 (−3.7%)	304 (−5.3%)	297 (−7.5%)	281* (−12.5%)
Relative liver weight (g/100 g)	2.69	2.75 (2.2%)	2.66 (−1.1%)	2.87** (6.7%)	3.21** (19.3%)	3.24** (20.4%)
Relative kidney weight (g/100 g)	0.69	0.76** (10.1%)	0.70 (1.4%)	0.76** (10.1%)	0.80** (15.9%)	0.77** (11.6%)
Females						
Number of animals	10	10	10	10	9	10
Average body weight (g)	190	197 (3.7%)	194 (2.1%)	193 (1.6%)	184 (−3.2%)	182 (−4.2%)
Relative liver weight (g/100 g)	2.82	2.84 (0.7%)	2.94 (4.3%)	3.04 (7.8%)	3.18** (12.8%)	3.36** (19.1%)
Relative kidney weight (g/100 g)	0.83	0.77 (−7.2%)	0.83 (0%)	0.83 (0%)	0.98* (18.1%)	0.93* (12.0%)

[a]Unspecified strain.
[b]Dow Chemical Co (1990, 1960).
*Significantly different from control ($p = 0.01$–0.05), statistical methods not reported by study authors.
**Significantly different from control ($p < 0.01$), statistical methods not reported by study authors.

Table B-4. Selected Effects on Male and Female CDF F344 Rats Exposed to FR-651A in Food for 13 Weeks[a,b]

Endpoint	Exposure Group (mg/kg-d)	
	0	600
Males		
Number of animals	10	10
Terminal body weight (g)	281 ± 31[c]	312 ± 23* (11.0%)
Terminal food consumption rate (g/day)	15 ± 2	18 ± 1*
Serum ALP (mU/mL)	88 ± 8	75 ± 4*
Serum ALT (mU/mL)	28 ± 2	27 ± 2
BUN (mg/100 mL)	23 ± 8	17 ± 2
Absolute liver weight (g)	7.23 ± 0.99	8.87 ± 0.71* (22.7%)
Relative liver weight (g/100 g)	2.82 ± 0.15	3.11 ± 0.21* (10.3%)
Absolute kidney weight (g)	1.79 ± 0.24	2.12 ± 0.18* (18.4%)
Relative kidney weight (g/100 g)	0.70 ± 0.03	0.74 ± 0.04* (5.7%)
Incidence of hepatocellular hypertrophy (very slight)	0/10[d]	10/10**
Decreased staining intensity of hepatocellular cytoplasm (very slight)	0/10	10/10**
Centrilobular hepatocellular necrosis with microfocal aggregates of RE cells (very slight to slight)	0/10	7/10**
Focal renal tubular degeneration and inflammation with or without fibrosis (very slight to slight)	3/10	9/10**
Females		
Number of animals	10	10
Terminal body weight (g)	202 ± 17	208 ± 17 (3.0%)
Food consumption rate (g/day)	12 ± 1	14 ± 1*
Serum ALP (AP; mU/mL)	55 ± 12	41 ± 17
Serum ALT (mU/mL)	26 ± 4	22 ± 4
BUN (mg/100 mL)	20 ± 4	15 ± 1*
Absolute liver weight (g)	5.01 ± 0.51	5.88 ± 0.58* (17.4%)
Relative liver weight (g/100 g)	2.72 ± 0.14	3.05 ± 0.18* (12.1%)
Absolute kidney weight (g)	1.35 ± 0.09	1.48 ± 0.13* (9.6%)
Relative kidney weight (g/100 g)	0.74 ± 0.05	0.77 ± 0.04 (4.1%)

Table B-4. Selected Effects on Male and Female CDF F344 Rats Exposed to FR-651A in Food for 13 Weeks[a,b]

Endpoint	Exposure Group (mg/kg-d)	
	0	600
Females		
Incidence of hepatocellular hypertrophy (very slight)	0/10	10/10**
Decreased staining intensity of hepatocellular cytoplasm (very slight)	0/10	10/10**
Centrilobular hepatocellular necrosis with microfocal aggregates of RE cells (very slight to slight)	0/10	0/10
Focal tubular degeneration and inflammation with or without fibrosis (very slight to slight)	1/10	0/10

[a]Dow Chemical Co (1980b, 1980c).
[b]The study authors noted recurrent mechanical problems with weighing apparatus used for food consumption measurements; thus, the doses estimated by the authors are uncertain. It is possible that body- and organ-weight measurements were also affected.
[c]Mean ± standard deviation.
[d]Number affected/number examined.
*Significantly different from control ($p < 0.05$) based on Dunnett's test, as reported by study authors.
**Significantly different from control ($p < 0.05$) based on Fisher's exact test performed for this review.

RE = reticulo-endothelial.

Table B-5. Selected Effects on Male and Female CDF F344 Rats Exposed to FR-651G in Food for 13 Weeks[a,b]

Endpoint	Exposure group (mg/kg-d)			
	0	10	30	100
Males				
Number of animals	15	10	10	10
Urine specific gravity	1.056 ± 0.006[c]	ND	ND	1.049 ± 0.003*
Absolute liver weight (g)	8.33 ± 0.80	7.90 ± 1.04	8.07 ± 0.64	9.11 ± 0.95
Relative liver weight (g/100 g)	3.01 ± 0.54	2.80 ± 0.15	2.87 ± 0.09	3.12 ± 0.11
Absolute kidney weight (g)	2.05 ± 0.11	1.98 ± 0.20	2.02 ± 0.17	2.13 ± 0.23
Relative kidney weight (g/100 g)	0.75 ± 0.15	0.70 ± 0.03	0.72 ± 0.03	0.73 ± 0.04
Liver swelling and decreased staining intensity of hepatocytes (very slight to slight)	0/10[d]	0/9	0/10	10/10**
Focal hepatocellular necrosis and inflammation (very slight)	0/10	0/9	0/10	1/10
Females				
Number of animals	15	10	10	10
Urine specific gravity	1.051 ± 0.008	ND	ND	1.054 ± 0.006
Absolute liver weight (g)	5.06 ± 0.57	5.04 ± 0.70	5.02 ± 0.45	5.48 ± 0.52
Relative liver weight (g/100 g)	2.67 ± 0.14	2.67 ± 0.13	2.75 ± 0.21	2.90 ± 0.11*
Absolute kidney weight (g)	1.38 ± 0.13	1.37 ± 0.15	1.37 ± 0.13	1.43 ± 0.11
Relative kidney weight (g/100 g)	0.73 ± 0.04	0.73 ± 0.04	0.76 ± 0.05	0.76 ± 0.04
Liver swelling and decreased staining intensity of hepatocytes (very slight to slight)	0/10	0/11	0/10	3/10
Focal hepatocellular necrosis and inflammation (very slight)	0/10	0/11	0/10	0/10

[a]Dow Chemical Co (1980d).
[b]The study authors noted recurrent mechanical problems with weighing apparatus used for food consumption measurements; thus, the doses estimated by the authors are uncertain. It is possible that body- and organ-weight measurements were also affected.
[c]Mean ± standard deviation.
[d]Number affected/number examined.
*Significantly different from control ($p < 0.05$) based on Dunnett's test, as reported by study authors.
**Significantly different from control ($p < 0.05$) based on Fisher's exact test performed for this review.

ND = no data.

Table B-6. Selected Effects on Male and Female CDF F344 Rats Exposed to FR-651 "Slurry Dried" in Food for 92 Days[a,b]

Endpoint	Exposure Group (mg/kg-d)			
	0	90	260	780
Males				
Number of animals per group	15	10	10	10
Terminal body weight (g)	324 ± 38[c]	302 ± 25 (−6.8%)	307 ± 20 (−5.2%)	269 ± 19* (−17.0%)
Food consumption, Days 85–92 (g/day)	17 ± 2	17 ± 1	18 ± 1	15 ± 1*
Serum ALT (mU/mL)	33 ± 4	32 ± 6	28 ± 4	28 ± 6
Serum ALP (mU/mL)	90 ± 10	78 ± 9*	75 ± 10*	70 ± 6*
BUN (mg/100 mL)	19 ± 2	17 ± 2	16 ± 2*	17 ± 3
Fasted body weight (g)	298 ± 38	277 ± 24 (−7.0%)	282 ± 19 (−5.4%)	247 ± 19* (−17.1%)
Absolute liver weight (g)	8.12 ± 0.83	8.57 ± 0.64 (5.5%)	9.46 ± 0.84* (16.5%)	8.51 ± 0.54 (4.8%)
Relative liver weight (g/100 g)	2.73 ± 0.15	3.10 ± 0.21* (13.6%)	3.35 ± 0.12* (22.7%)	3.45 ± 0.14* (26.4%)
Absolute kidney weight (g)	2.05 ± 0.17	2.02 ± 0.15 (−1.5%)	2.08 ± 0.13 (1.5%)	1.94 ± 0.13 (−5.4%)
Relative kidney weight (g/100 g)	0.69 ± 0.05	0.73 ± 0.03 (5.8%)	0.74 ± 0.02* (7.2%)	0.79 ± 0.04* (14.5%)
Hepatocellular hypertrophy (very slight to slight)	0/10[d]	0/10	10/10**	0/10
Hepatocellular hypertrophy (slight to moderate)	0/10	0/10	0/10	10/10**
Altered appearance and staining intensity of hepatocellular cytoplasm (very slight to slight)	0/10	0/10	1/10	0/10
Altered appearance and staining intensity of hepatocellular cytoplasm (slight to moderate)	0/10	0/10	0/10	9/10**
Focal hepatocellular necrosis and inflammation (very slight)	0/10	0/10	0/10	1/10
Females				
Number of animals per group	15	10	10	10
Terminal body weight (g)	203 ± 17	200 ± 15 (−1.5%)	207 ± 15 (2.0%)	187 ± 10* (−7.9%)
Food consumption, Days 85–92 (g/day)	13 ± 1	14 ± 2	14 ± 1	13 ± 1
Serum ALT (mU/mL)	26 ± 4	21 ± 3	22 ± 6	15 ± 2*
Serum ALP (mU/mL)	51 ± 12	47 ± 10	35 ± 11*	36 ± 7*
BUN (mg/100 mL)	17 ± 2	18 ± 12	14 ± 2	16 ± 2
Fasted body weight (g)	185 ± 16	189 ± 15 (2.2%)	190 ± 14 (2.7%)	170 ± 9* (−8.1%)

Table B-6. Selected Effects on Male and Female CDF F344 Rats Exposed to FR-651 "Slurry Dried" in Food for 92 Days[a,b]

Endpoint	Exposure Group (mg/kg-d)			
	0	90	260	780
Females				
Absolute liver weight (g)	4.93 ± 0.50	5.02 ± 0.44 (1.8%)	5.82 ± 0.39* (18.1%)	5.86 ± 0.28* (18.9%)
Relative liver weight (g/100 g)	2.66 ± 0.16	2.67 ± 0.26 (0.4%)	3.08 ± 0.18* (15.8%)	3.45 ± 0.14* (29.7%)
Absolute kidney weight (g)	1.30 ± 0.11	1.34 ± 0.10 (3.1%)	1.39 ± 0.08 (6.9%)	1.38 ± 0.07 (6.2%)
Relative kidney weight (g/100 g)	0.71 ± 0.05	0.72 ± 0.06 (1.4%)	0.74 ± 0.04 (4.2%)	0.81 ± 0.04* (14.1%)
Hepatocellular hypertrophy (very slight to slight)	0/10	0/10	10/10**	10/10**
Hepatocellular hypertrophy (slight to moderate)	0/10	0/10	0/10	0/10
Altered appearance and staining intensity of hepatocellular cytoplasm (very slight to slight)	0/10	0/10	2/10	3/10
Altered appearance and staining intensity of hepatocellular cytoplasm (slight to moderate)	0/10	0/10	0/10	0/10
Focal hepatocellular necrosis and inflammation (very slight)	0/10	0/10	0/10	0/10

[a]Dow Chemical Co (1980a).
[b]The study authors noted recurrent mechanical problems with weighing apparatus used for food consumption measurements; thus, the doses estimated by the authors are uncertain. It is possible that body- and organ-weight measurements were also affected.
[c]Mean ± standard deviation.
[d]Number affected/number examined.
*Significantly different from control ($p < 0.05$) based on Dunnett's test, as reported by study authors.
**Significantly different from control ($p < 0.05$) based on Fisher's exact test performed for this review.

Table B-7. Selected Effects on Male and Female F344 Rats Exposed to FR-651A in Food for 2 Years[a]

Males				
	Exposure Group (mg/kg-d)			
Endpoint	**0**	**1**	**15**	**50**
Number of animals	86	50	50	50
Terminal body weight (g)	423 ± 25[b]	416 ± 25 (−1.7%)	417 ± 33 (−1.4%)	405 ± 20* (−4.3%)
Urine specific gravity	1.051 ± 0.011	1.047 ± 0.009	1.043 ± 0.008	1.037 ± 0.007*
Interim sacrifice (10 rats/group)				
Absolute liver weight (g)	8.88 ± 0.55	9.42 ± 0.67 (6.1%)	9.80 ± 0.67* (10.4%)	10.01 ± 1.18* (12.7%)
Relative liver weight (g/100 g)	2.36 ± 0.10	2.47 ± 0.11 (4.7%)	2.48 ± 0.12 (5.1%)	2.63 ± 0.26* (11.4%)
Absolute kidney weight (g)	2.57 ± 0.10	2.58 ± 0.12 (0.4%)	2.70 ± 0.17 (5.1%)	2.70 ± 0.13 (5.1%)
Relative kidney weight (g/100 g)	0.68 ± 0.03	0.68 ± 0.02 (0%)	0.68 ± 0.02 (0%)	0.71 ± 0.02 (4.4%)
Terminal sacrifice (18–20 rats/group)				
Absolute liver weight (g)	11.65 ± 1.90	11.28 ± 0.87 (−3.2%)	11.84 ± 1.25 (1.6%)	12.28 ± 1.73 (5.4%)
Relative liver weight (g/100 g)	2.94 ± 0.50	2.89 ± 0.45 (−1.7%)	2.93 ± 0.32 (−0.3%)	3.15 ± 0.44 (7.1%)
Absolute kidney weight (g)	3.04 ± 0.24	2.91 ± 0.15 (−4.3%)	3.12 ± 0.32 (2.6%)	3.04 ± 0.19 (0%)
Relative kidney weight (g/100 g)	0.77 ± 0.08	0.74 ± 0.09 (−3.9%)	0.77 ± 0.09 (0%)	0.78 ± 0.05 (1.3%)
Females				
	Exposure Group (mg/kg-d)			
Endpoint	**0**	**1**	**20**	**70**
Number of animals	86	50	50	50
Terminal body weight (g)	300 ± 25	297 ± 27 (−1.0%)	299 ± 20 (−0.3%)	284 ± 27* (−5.3%)
Urine specific gravity	1.040 ± 0.004	1.038 ± 0.011	1.047 ± 0.008	1.044 ± 0.017
Interim sacrifice (10 rats/group)				
Absolute liver weight (g)	5.70 ± 0.43	5.93 ± 0.43 (4.0%)	6.16 ± 0.57 (8.1%)	6.20 ± 0.54 (8.8%)
Relative liver weight (g/100 g)	2.62 ± 0.09	2.69 ± 0.10 (2.7%)	2.84 ± 0.25* (8.4%)	2.81 ± 0.09* (7.3%)
Absolute kidney weight (g)	1.69 ± 0.09	1.73 ± 0.09 (2.4%)	1.72 ± 0.09 (1.8%)	1.78 ± 0.16 (5.3%)
Relative kidney weight (g/100 g)	0.78 ± 0.03	0.79 ± 0.03 (1.3%)	0.79 ± 0.04 (1.3%)	0.81 ± 0.34 (3.8%)

Table B-7. Selected Effects on Male and Female F344 Rats Exposed to FR-651A in Food for 2 Years[a]

Females				
Terminal sacrifice (18–20 rats/group)				
Absolute liver weight (g)	8.01 ± 1.03	7.99 ± 0.79 (−0.2%)	8.61 ± 1.46 (7.5%)	8.48 ± 1.24 (5.9%)
Relative liver weight (g/100 g)	2.86 ± 0.59	2.89 ± 0.43 (1.0%)	3.06 ± 0.64 (7.0%)	3.17 ± 0.48 (10.8%)
Absolute kidney weight (g)	2.25 ± 0.30	2.18 ± 0.19 (−3.1%)	2.35 ± 0.43 (4.4%)	2.31 ± 0.33 (2.7%)
Relative kidney weight (g/100 g)	0.81 ± 0.19	0.79 ± 0.12 (−2.5%)	0.84 ± 0.23 (3.7%)	0.86 ± 0.11 (6.2%)

[a]Dow Chemical Co (1983a, 1983b).
[b]Mean ± standard deviation.
*Significantly different from control ($p < 0.05$) based on Dunnett's test, as reported by the study authors.

Table B-8. Incidences of Selected Histopathological Observations (Non-neoplastic Lesions) of Male and Female F344 Rats Exposed to FR-651A in Food for 2 Years[a]

Males				
	Exposure Group (mg/kg-d)			
Endpoint	**0**	**1**	**15**	**50**
Interim sacrifice				
Altered tinctorial properties of hepatocytes, multifocal	0/10[b]	0/10	0/10	9/10**
Multifocal hepatocellular hypertrophy	0/10	0/10	0/10	9/10**
Terminal sacrifice[c]				
Dilatation, hypercellularity, and aggregates of cellular debris in intestinal crypts	0/84	0/50	2/50	8/49*
Females				
	Exposure Group (mg/kg-d)			
Endpoint	**0**	**1**	**20**	**70**
Interim sacrifice				
Altered tinctorial properties of hepatocytes, multifocal	0/10	0/10	0/10	0/10
Multifocal hepatocellular hypertrophy	0/10	0/10	0/10	0/10
Terminal sacrifice[c]				
Dilatation, hypercellularity, and aggregates of cellular debris in intestinal crypts	1/86	0/49	1/50	11/50*

[a]Dow Chemical Co (1983a, 1983b).
[b]Number affected/number examined.
[c]Histopathology examination at terminal sacrifice was limited to tissues of the gastrointestinal tract.
*Significantly different from control ($p < 0.05$), by Fisher's exact test as reported by the study authors.
**Significantly different from control ($p < 0.05$), by Fisher's exact test conducted for this review.

Table B-9. Incidences of Neoplastic Lesions of Large Intestine in Male and Female F344 Rats Exposed to FR-651A in Food for 2 Years[a]

Males				
	Exposure Group (mg/kg-d)			
Endpoint	0	1	15	50
Polypoid adenoma	1/84	1/50	0/50	5/49*
Polypoid adenocarcinoma	0/84	0/50	0/50	1/49
Polypoid adenoma and/or adenocarcinoma	1/84	1/50	0/50	5/49*
Females				
	Exposure Group (mg/kg-d)			
Endpoint	0	1	20	70
Polypoid adenoma	1/86	0/49	3/50	8/50*
Polypoid adenocarcinoma	0/86	0/49	0/50	1/50
Polypoid adenoma and/or adenocarcinoma	1/86	0/49	3/50	9/50*

[a]Dow Chemical Co (1983a, 1983b).
*Significantly different from control ($p < 0.05$), by Fisher's exact test as reported by the study authors.

Table B-10. Incidences of Neoplastic Lesions of Large Intestine in Male and Female F344 Rats Exposed to FR-651C in Food for 2 Years[a]

Males				
	Exposure Group (mg/kg-d)			
Endpoint	0	1	15	50
Polypoid adenoma	1/83	0/49	1/50	2/48
Polypoid adenocarcinoma	0/83	0/49	1/50	0/48
Polypoid adenoma and/or adenocarcinoma	1/83	0/49	2/50	2/48
Females				
	Exposure Group (mg/kg-d)			
Endpoint	0	1	20	70
Polypoid adenoma	2/85	0/50	2/50	8/50*
Polypoid adenocarcinoma	0/85	0/50	0/50	1/50
Polypoid adenoma and/or adenocarcinoma	2/85	0/50	2/50	9/50*

[a]Keyes et al. (1982) as cited in U.S. EPA (1985).
*Significantly different from control ($p < 0.05$), by Fisher's exact test (one sided) as reported by the study authors.

APPENDIX C. BENCHMARK DOSE MODELING RESULTS

MODELING PROCEDURE FOR DICHOTOMOUS DATA

Benchmark dose (BMD) modeling of dichotomous data was conducted with the EPA's BMD software (BMDS, Version 2.5). For these data, the gamma, logistic, log logistic, log-probit, multistage, probit, and Weibull dichotomous models available within the software were fit using a benchmark response (BMR) of 10% extra risk. Adequacy of model fit was judged based on the χ^2 goodness-of-fit p-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all of the models providing adequate fit, the benchmark dose lower confidence limit (BMDL) from the model with the lowest Akaike's information criterion (AIC) was selected as a potential point of departure (POD) when BMDL values were within a factor of 2–3. When BMDL values from models providing adequate fit varied more than two or threefold, the lowest BMDL was selected as a potential POD.

Model Predictions for Lesions of the Intestinal Crypts in F344 Rats Given FR-651A in the Diet for 2 Years

All available quantal models in BMDS (Version 2.5) were fit to the data on lesions of the intestinal crypts (dilatation, hypercellularity, and aggregates of cellular debris) in male and female rats (Dow Chemical Co, 1983a, b) (see Table C-1). BMD modeling was performed using the doses administered in the study. A default BMR of 10% extra risk was used in the BMD modeling.

Table C-1. Incidences of Intestinal Lesions in Male and Female F344 Rats Exposed to FR-651A in Food for 2 Years[a]

Males				
Endpoint	Exposure Group (mg/kg-d)			
	0	1	15	50
Terminal sacrifice				
Dilatation, hypercellularity, and aggregates of cellular debris in intestinal crypts	0/84[b]	0/50	2/50	8/49*
Females				
Endpoint	Exposure Group (mg/kg-d)			
	0	1	20	70
Terminal sacrifice				
Dilatation, hypercellularity, and aggregates of cellular debris in intestinal crypts	1/86	0/49	1/50	11/50*

[a]Dow Chemical Co (1983a, 1983b).
[b]Number affected/number examined.
*Significantly different from control ($p < 0.05$), as reported by the study authors.

For male rat data, all of the available models provided adequate fit ($p > 0.1$; see Table C-2), and scaled residuals at the dose closest to the BMR were acceptable for all models. BMDLs from all models were within a factor of three, so the model with the lowest AIC was selected. The 1-degree multistage model exhibited the lowest AIC (see Table C-2). The BMD_{10} and $BMDL_{10}$ values from this model were 32 and 20 mg/kg-day, respectively. The $BMDL_{10}$ from this study was selected as the POD for deriving the screening chronic p-RfD. Figure C-1 shows the model fit to the data.

Table C-2. BMD Model Results from Incidence of Dilation, Hypercellularity, and Aggregates of Cellular Debris in Intestinal Crypts in Male F344 Rats[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-value[b]	Scaled Residuals[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[d]	2	0.07	0.97	−0.05	64.52	32.91	20.35
Logistic	2	2.44	0.30	−0.13	67.22	42.16	35.20
Log-logistic[e]	2	0.06	0.97	−0.04	64.52	32.72	19.58
Log-probit[e]	3	1.43	0.70	−0.53	63.58	33.00	24.63
Multistage (1-degree)[f,g]	**3**	**0.29**	**0.96**	**−0.27**	**62.86**	**31.92**	**19.76**
Multistage (2-degree)[f]	2	0.12	0.94	−0.03	64.63	34.08	20.16
Multistage (3-degree)[f]	2	0.12	0.94	−0.03	64.63	34.08	20.16
Probit	2	2.06	0.36	−0.17	66.79	40.49	32.95
Weibull[d]	2	0.07	0.96	−0.04	64.53	33.11	20.33

[a]Dow Chemical Co (1983a, 1983b).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by less than two- to three-fold), so the model with the lowest AIC was selected (1-degree multistage).

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response [i.e., $_{10}$ = dose associated with 10% extra risk]); DF = degree(s) of freedom.

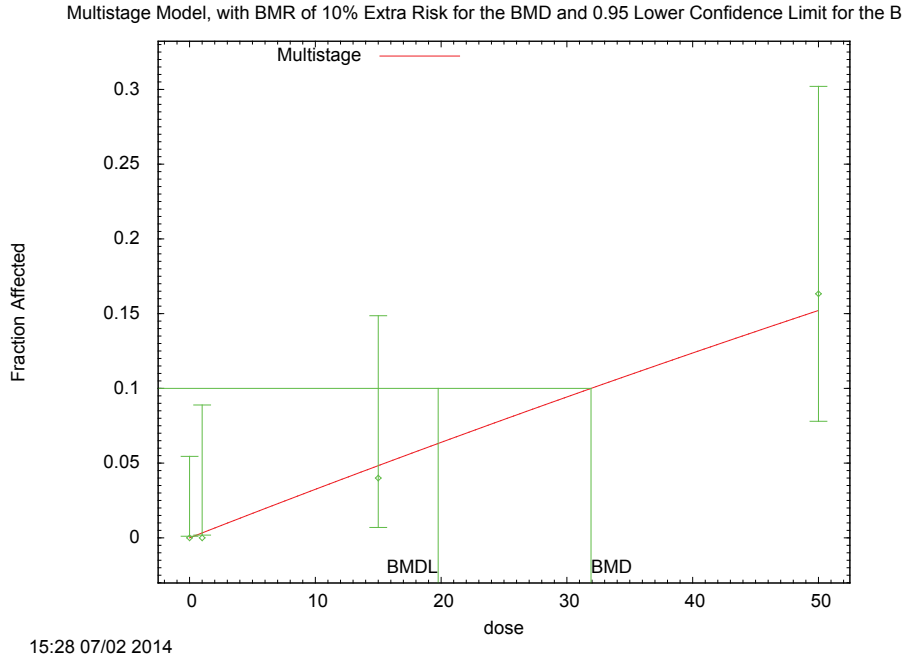

Figure C-1. Fit of Selected Model to Data on Intestinal Lesions in Male F344 Rats

```
 ======================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/USEPA/PTV/FR651A/intestinalcrypts/male/mst_intestinalcrypts_male_multi1.(d)
        Gnuplot Plotting File:
C:/USEPA/PTV/FR651A/intestinalcrypts/male/mst_intestinalcrypts_male_multi1.plt
                                          Wed Jul 02 15:28:45 2014
 ======================================================================

 BMDS_Model_Run
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   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 = 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
                        Beta(1) =   0.00361031
```

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	*	*	*
Beta(1)	0.00330101	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-30.2044	4			
Fitted model	-30.4323	1	0.455702	3	0.9285
Reduced model	-41.2668	1	22.1248	3	<.0001

AIC: 62.8645

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	84.000	0.000
1.0000	0.0033	0.165	0.000	50.000	-0.407
15.0000	0.0483	2.415	2.000	50.000	-0.274
50.0000	0.1521	7.455	8.000	49.000	0.217

Chi^2 = 0.29 d.f. = 3 P-value = 0.9624

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 31.9176

BMDL = 19.7645

BMDU = 56.4295

Taken together, (19.7645, 56.4295) is a 90 % two-sided confidence interval for the BMD

For female rat data, all of the available models provided adequate fit ($p > 0.1$; see Table C-3), and scaled residuals at the dose closest to the BMR were acceptable for all models. BMDLs from all models were within a factor of three, so the model with the lowest AIC was selected. The logistic model exhibited the lowest AIC (see Table C-3). The BMD_{10} and $BMDL_{10}$ values from this model were 54 and 45 mg/kg-day, respectively. Figure C-2 shows the model fit to the data.

Table C-3. BMD Model Results from Incidence of Dilatation, Hypercellularity, and Aggregates of Cellular Debris in Intestinal Crypts in Female F344 Rats[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-value[b]	Scaled Residuals[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Gamma[d]	1	0.57	0.45	0	80.30	47.87	30.99
Logistic[e]	**2**	**0.61**	**0.74**	**0.003**	**78.34**	**53.53**	**44.84**
Log-logistic[f]	1	0.57	0.45	0	80.30	48.47	30.64
Log-probit[f]	1	0.57	0.45	0	80.30	45.77	32.73
Multistage (1-degree)[g]	2	2.73	0.25	−1.20	80.95	37.77	23.93
Multistage (2-degree)[g]	2	0.7	0.71	0.07	78.39	46.73	31.88
Multistage (3-degree)[g]	1	0.57	0.45	0	80.30	49.97	32.24
Probit	2	0.7	0.70	0.02	78.38	50.61	41.44
Weibull[d]	1	0.57	0.45	0	80.30	49.22	31.18

[a]Dow Chemical Co (1983a, 1983b).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMD.
[d]Power restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by less than two- to three-fold), so the model with the lowest AIC was selected (Logistic).
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike's information criterion; BMD = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response [i.e., $_{10}$ = dose associated with 10% extra risk]); DF = degree(s) of freedom.

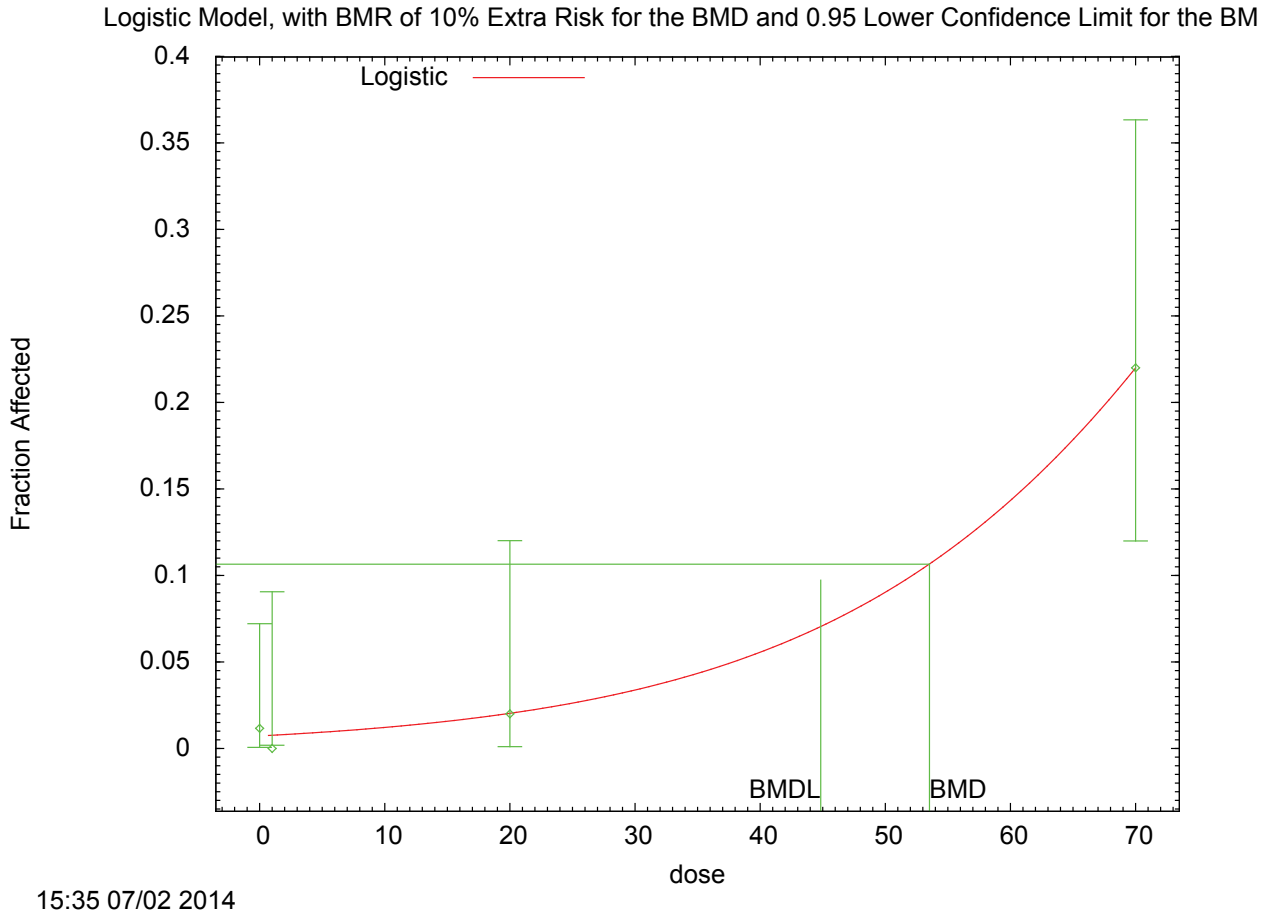

Figure C-2. Fit of Selected Model to Data on Intestinal Lesions in Female F344 Rats

```
 ======================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File:
C:/USEPA/PTV/FR651A/intestinalcrypts/female/log_intestinalcrypts_female_Log-BMR10.(d)
        Gnuplot Plotting File:
C:/USEPA/PTV/FR651A/intestinalcrypts/female/log_intestinalcrypts_female_Log-BMR10.plt
                                          Wed Jul 02 15:35:01 2014
 ======================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = 1/[1+EXP(-intercept-slope*dose)]

   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is not restricted

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

```
                 Default Initial Parameter Values
                    background =            0   Specified
                     intercept =     -4.35077
                         slope =    0.0443347

          Asymptotic Correlation Matrix of Parameter Estimates

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

              intercept        slope

 intercept            1        -0.93

     slope        -0.93            1

                                Parameter Estimates

                                                                95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
      intercept         -4.92187
0.822186            -6.53333            -3.31042
          slope        0.0522159        0.0129709           0.0267935
0.0776384

                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -36.6959         4
   Fitted model         -37.1683         2      0.944869      2          0.6235
  Reduced model         -50.2639         1        27.136      3         <.0001

          AIC:          78.3366
                                 Goodness  of  Fit
                                                                      Scaled
     Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0072         0.622     1.000          86        0.481
    1.0000     0.0076         0.373     0.000          49       -0.613
   20.0000     0.0203         1.014     1.000          50       -0.014
   70.0000     0.2198        10.991    11.000          50        0.003

 Chi^2 = 0.61      d.f. = 2        P-value = 0.7380

   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        53.5272

            BMDL =        44.8415
```

Model Predictions for Polypoid Adenomas and Adenocarcinomas in F344 Rats Given FR-651A in the Diet for 2 Years

BMD modeling of the incidences of polypoid adenoma or adenocarcinoma of the intestines in male and female rats exposed to FR-651A for 2 years was performed using the procedure outlined above, with a slight modification: only the multistage model is applied to cancer data sets. The incidences of intestinal tumors are shown in Table C-4 below. A default BMR of 10% extra risk was used in the BMD modeling.

Table C-4. Incidences of Intestinal Tumors in Male and Female F344 Rats Exposed to FR-651A in Food for 2 Years[a]

Males				
	Animal Dose (mg/kg-d)			
Endpoint	**0**	**1**	**15**	**50**
Polypoid adenoma and/or adenocarcinoma	1/84	1/50	0/50	5/49*
Females				
	Animal Dose (mg/kg-d)			
Endpoint	**0**	**1**	**20**	**70**
Polypoid adenoma and/or adenocarcinoma	1/86	0/49	3/50	9/50*

[a]Dow Chemical Co (1983a, 1983b).
*Significantly different from control ($p < 0.05$), as reported by study authors.

For the data in female rats, all of the available models provided adequate fit ($p > 0.1$; see Table C-5), and scaled residuals at the dose closest to the BMR were acceptable for all models. The 1-degree multistage model exhibited the lowest AIC (see Table C-5). The BMD_{10} (HED) and $BMDL_{10}$ (HED) values from this model were 9.5 and 5.9 mg/kg-day, respectively. The $BMDL_{10}$ (HED) of 5.9 mg/kg-day was selected as the POD for deriving the screening cancer potency value. Figure C-3 shows the model fit to the data.

Table C-5. BMD Model Results from Incidence of Polypoid Adenoma and/or Adenocarcinoma in Female F344 Rats[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-value[b]	Scaled Residuals[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Multistage (1-degree)[d,e]	**2**	**0.68**	**0.71**	**0.03**	**85.86**	**9.46**	**5.93**
Multistage (2-degree)[d]	1	0.68	0.41	0.10	87.85	9.69	5.93
Multistage (3-degree)[d]	1	0.68	0.41	0.10	87.85	9.69	5.93

[a]Dow Chemical Co (1983a, 1983b).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMD.
[d]Betas restricted to ≥0.
[e]Selected model All models provided adequate fit to the data. BMDLs for models providing adequate fit were nearly identical, so the model with the lowest AIC was selected (1-degree multistage).

AIC = Akaike's information criterion; BMD_{10} = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response [i.e., $_{10}$ = dose associated with 10% extra risk]); DF = degree(s) of freedom.

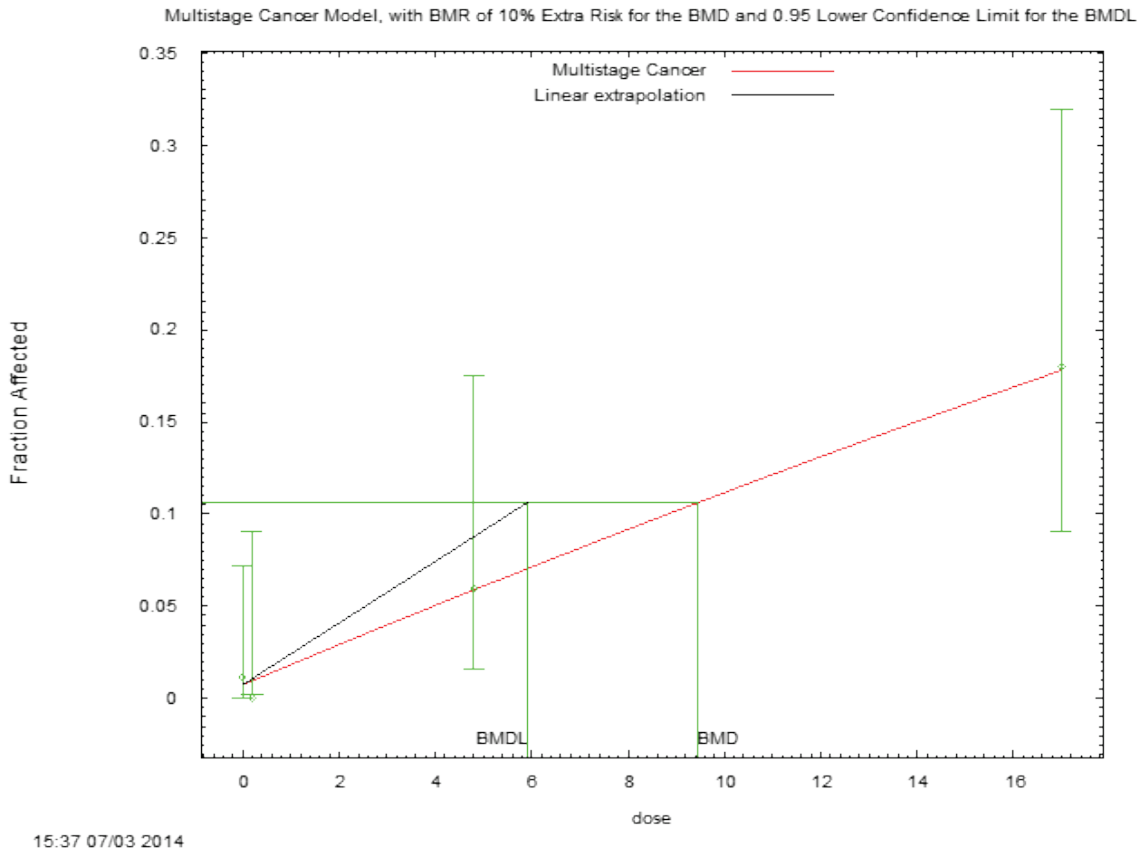

Figure C-3. Fit of Selected Model to Data on Intestinal Tumor Incidences in Females

```
=================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/USEPA/PTV/FR651A/polyploid_adeno_adenocarc/female/msc_neoplasm_female_Msc1-
BMR10.(d)
        Gnuplot Plotting File:
C:/USEPA/PTV/FR651A/polyploid_adeno_adenocarc/female/msc_neoplasm_female_Msc1-
BMR10.plt
                                              Thu Jul 03 15:37:18 2014
 =================================================================

 BMDS_Model_Run
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   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 = 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 =    0.0053994
                       Beta(1) =    0.0113803

           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       0.00746827           *               *                 *
        Beta(1)        0.0111378           *               *                 *

* - Indicates that this value is not calculated.

                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -40.3666         4
   Fitted model         -40.9294         2       1.12573      2          0.5696
  Reduced model         -50.2639         1       19.7946      3       0.0001872
```

AIC: 85.8589

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0075	0.642	1.000	86.000	0.448
0.2000	0.0097	0.474	0.000	49.000	-0.692
4.8000	0.0591	2.957	3.000	50.000	0.026
17.0000	0.1787	8.934	9.000	50.000	0.024

Chi^2 = 0.68 d.f. = 2 P-value = 0.7115

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 9.45977

BMDL = 5.93052

BMDU = 17.0663

Taken together, (5.93052, 17.0663) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.0168619

For the data in male rats, all of the available models provided adequate fit ($p > 0.1$; see Table C-6), and scaled residuals at the dose closest to the BMR were acceptable for all models. The 3-degree multistage model exhibited the lowest AIC (see Table C-6). The BMD_{10} (HED) and $BMDL_{10}$ (HED) values from this model were 15 and 11 mg/kg-day, respectively. Figure C-4 shows the model fit to the data.

Table C-6. BMD Model Results from Incidence of Polypoid Adenoma and/or Adenocarcinoma in Male F344 Rats[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-value[b]	Scaled Residuals[c]	AIC	BMD_{10} (mg/kg-d)	$BMDL_{10}$ (mg/kg-d)
Multistage (1-degree)[d]	2	2.20	0.33	0.59	60.67	20.61	9.86
Multistage (2-degree)[d]	2	1.34	0.51	0.20	59.15	15.37	10.73
Multistage (3-degree)[d,e]	**2**	**1.06**	**0.59**	**0.06**	**58.60**	**14.55**	**11.09**

[a]Dow Chemical Co (1983a, 1983b).
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMD.
[d]Betas restricted to ≥0.
[e]Selected model. All models provided adequate fit to the data. BMDLs for models providing adequate fit were sufficiently close (differed by less than two- to three-fold), so the model with the lowest AIC was selected (3-degree multistage).

AIC = Akaike's information criterion; BMD_{10} = maximum likelihood estimate of the dose associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response [i.e., $_{10}$ = dose associated with 10% extra risk]); DF = degree(s) of freedom.

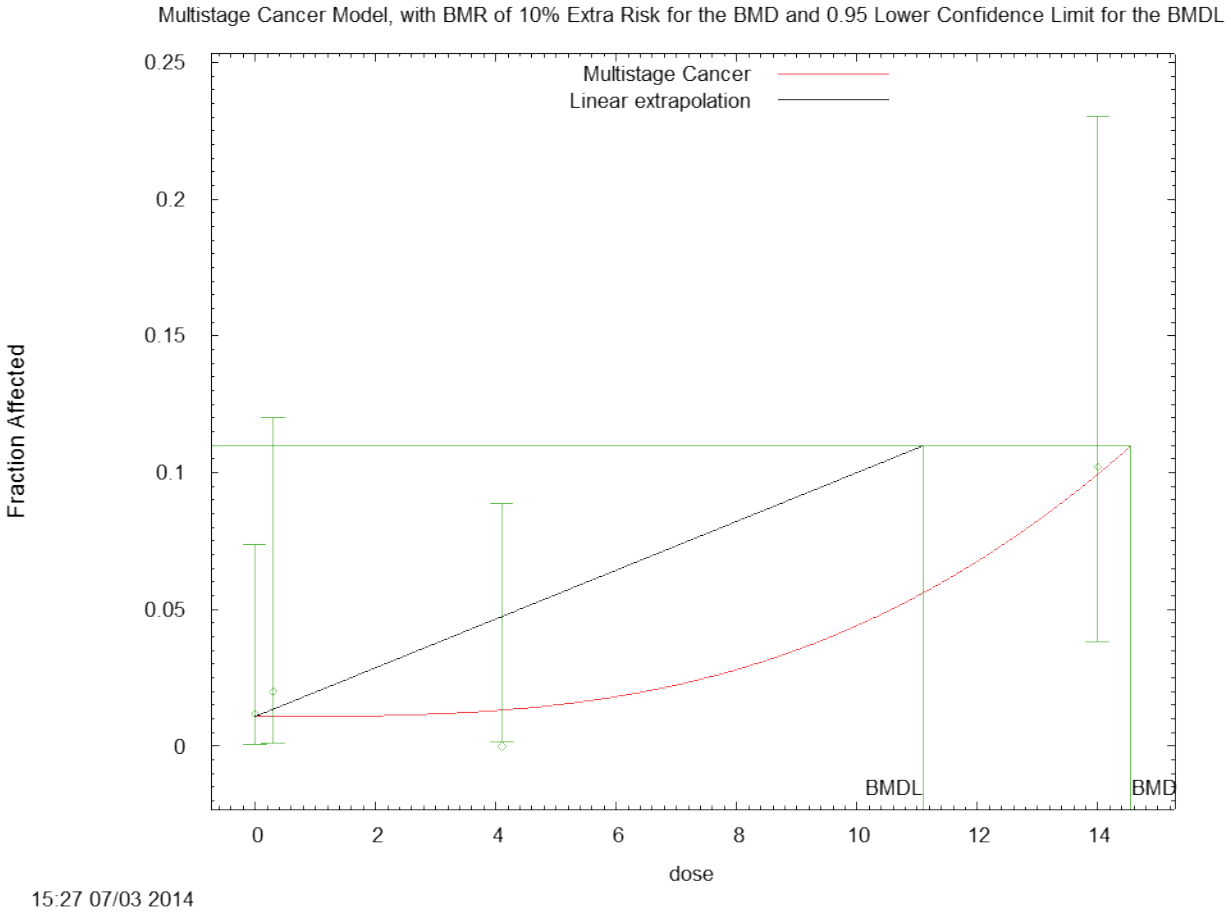

Figure C-4. Fit of Selected Model to Data on Intestinal Tumor Incidences in Males

```
 ================================================================
        Multistage Model. (Version: 3.4;  Date: 05/02/2014)
        Input Data File:
C:/USEPA/PTV/FR651A/polyploid_adeno_adenocarc/male/msc_neoplasm_male_Msc3-BMR10.(d)
        Gnuplot Plotting File:
C:/USEPA/PTV/FR651A/polyploid_adeno_adenocarc/male/msc_neoplasm_male_Msc3-BMR10.plt
                                                Thu Jul 03 15:27:45 2014
 ================================================================

 BMDS_Model_Run
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   The form of the probability function is:

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

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 0
 Degree of polynomial = 3


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



                  Default Initial Parameter Values
                     Background =   0.00996563
                        Beta(1) =            0
                        Beta(2) =            0
                        Beta(3) =   3.546e-005


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Beta(1)    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

             Background      Beta(3)

Background            1        -0.45

   Beta(3)        -0.45            1



                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
```

Background	0.0109438	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0	*	*	*
Beta(3)	3.41808e-005	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-26.4745	4			
Fitted model	-27.2999	2	1.65086	2	0.438
Reduced model	-31.4297	1	9.91044	3	0.01934

AIC: 58.5998

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0109	0.919	1.000	84.000	0.085
0.3000	0.0109	0.547	1.000	50.000	0.615
4.1000	0.0133	0.664	0.000	50.000	-0.820
14.0000	0.0995	4.875	5.000	49.000	0.060

Chi^2 = 1.06 d.f. = 2 P-value = 0.5880

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 14.5534

BMDL = 11.0934

BMDU = 33.3989

Taken together, (11.0934, 33.3989) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.00901439

APPENDIX D. REFERENCES

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