FINAL

Report on Carcinogens Background Document for

2,3-Dibromo-1-propanol

Meeting of the
NTP Board of Scientific Counselors
Report on Carcinogens Subcommittee

Prepared for the:
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Criteria for Listing Agents, Substances or Mixtures in the Report on Carcinogens

US Department of Health and Human Services
National Toxicology Program

Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated to be Human Carcinogens:

There is limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species, or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a *known to be human carcinogen, or reasonably anticipated to be human carcinogen* or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Summary Statement

2,3-Dibromo-1-propanol

CASRN 96-13-9

Carcinogenicity

2,3-Dibromo-1-propanol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in rats and mice (NTP 1993).

2,3-Dibromo-1-propanol administered to rats by skin painting for up to 55 weeks induced increased incidences of tumors of the skin, nasal mucosa, digestive tract, Zymbal gland, liver, kidney, tunica vaginalis, and spleen. Mice similarly exposed for up to 42 weeks exhibited increased incidences of tumors of skin, forestomach, liver, and lung.

No case reports or epidemiological studies of the occurrence of human cancer and exposure to 2,3-dibromo-1-propanol were found.

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

2,3-Dibromo-1-propanol demonstrated genotoxicity in *in vitro* and *in vivo* systems including *Salmonella typhimurium*, *Escherichia coli*, V79 hamster cell, and mouse lymphoma cell mutation assays. It also induced sex-linked recessive lethal mutations and reciprocal translocations in *Drosophila melanogaster*. Chromosomal aberrations were induced in Chinese hamster ovary cells *in vitro*, but micronuclei were not induced in the bone marrow of mice administered 2,3-dibromo-1-propanol by injection.

No data are available to suggest that the mechanisms thought to account for tumor induction by this agent in experimental animals would not operate in humans.

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1 Introduction

2,3-Dibromo-1-propanol (DBP) was nominated for listing in the Report on Carcinogens (RoC) by the National Institute of Environmental Health Sciences (NIEHS) RoC Review Group (RG1) based on the results of a skin painting study reported in a 1993 National Toxicology Program (NTP) bioassay technical report that indicated clear evidence of carcinogenicity in rats and mice (NTP 1993).

1.1 Chemical identification

DBP ($C_3H_6Br_2O$, mol wt 217.89, CASRN 96-13-9) also is known by the following names:

glycerol 1,2-dibromohydrin
beta-dibromohydrin
dibromopropanol
allyl alcohol dibromide.

DBP is a halogenated aliphatic alcohol used as a chemical intermediate in the synthesis of flame retardants, insecticides, and pharmaceuticals. It is a clear, colorless, viscous liquid. The structure of DBP is illustrated in Figure 1-1.

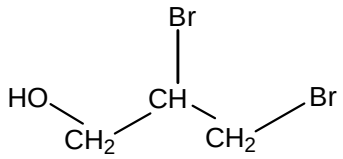

Figure 1-1. Structure of DBP

1.2 Physical-chemical properties

DBP is incompatible with strong oxidizers (Radian 1991). Its RTECS number is UB0175000. The physical and chemical properties of DBP are summarized in Table 1-1.

Table 1-1. Physical and chemical properties of DBP

Property	Information	Reference
Molecular weight	217.89	CRC (1998)
Color	colorless	CRC (1998)
Physical state	viscous liquid	CRC (1998)
Boiling point (°C)	219	CRC (1998
Flash point (°C)	112	Lenga (1985)
Specific gravity	2.12	Chemfinder (1999); Radian (1991)
Density (g/mL)	2.12	Lenga (1985); Aldrich (1988)

Property	Information	Reference
Solubility at 20°C in:		
Water	50 - 100 mg/mL	Radian (1991)
Dimethylsulfoxide	≥ 100 mg/mL	Radian (1991)
95% Ethanol	≥ 100 mg/mL	Radian (1991)
Acetone	≥ 100 mg/mL	Radian (1991)

1.3 Identification of metabolites

DBP is a metabolite of the flame retardant tris(2,3-dibromopropyl)phosphate (TRIS-BP) ($C_9H_{15}Br_6O_4P$, mol wt 697.61, CASRN 126-72-7). TRIS-BP is a viscous, pale yellow liquid that is slightly soluble in water and is hydrolyzed by acids and bases. The RTECS number for TRIS-BP is UB0350000 and the U.S. Environmental Protection Agency (EPA) hazardous waste number is U235 (HSDB 1998). The structure of TRIS-BP is illustrated in Figure 1-2.

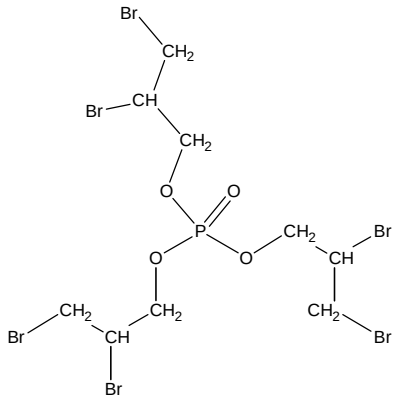

Figure 1-2. Structure of TRIS-BP

DBP undergoes oxidation, followed by dehydrohalogenation, to yield 2-bromoacrolein, an unstable intermediate leading to the formation of bromoacrylic acid (Marsden and Casida 1982, cited in NTP 1993). The structure of 2-bromoacrolein (C_3H_3BrO, mol wt 134.96) is shown in Figure 1-3 and the structure of bromoacrylic acid ($C_3H_3BrO_2$, mol wt 150.95) is shown in Figure 1-4.

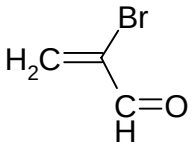

Figure 1-3. Structure of 2-bromoacrolein

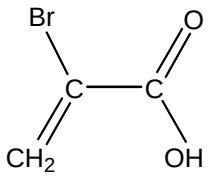

Figure 1-4. Structure of bromoacrylic acid

DBP also may be oxidized to 3-bromo-1,2-propane epoxide (Jones and Fakhouri 1979, cited in NTP 1993). The structure of this epoxybromopropane (C_3H_5BrO mol wt 136.97) is shown in Figure 1-5.

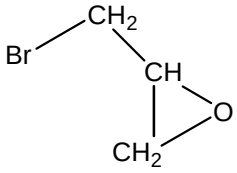

Figure 1-5. Structure of 3-bromo-1,2-propane epoxide

2 Human Exposure

2.1 Use

The major use of DBP is as an intermediate in the production of flame retardants, insecticides, and pharmaceuticals. DBP was previously used in the production of TRIS-BP, a flame retardant used in children's clothing and other products (NTP 1998). All domestic production of TRIS-BP was banned in 1978 (Radian 1991 and HSDB 1998).

2.2 Production

Only one U.S. producer of DBP, Great Lakes Chemical Corporation was identified, but production levels were not given (SRI 1989, cited by HSDB 1998). U.S. production of DBP was greater than 10 million lb in 1976 (Fishbein 1979). Sleepwear containing DBP and TRIS-BP was banned in 1977, after studies showed that DBP was mutagenic in bacteria and TRIS-BP was mutagenic and carcinogenic in rats. Production of DBP decreased drastically after the ban. Current production values have not been reported (NTP 1993). U.S. EPA, in 1994, reported the U.S. production of DBP to be < 1 million lb, and it was not listed in the high production volume (HPV) chemical list (U.S. EPA 1994).

2.3 Analysis

DBP is detected in urine via a negative ion mass spectrometry method (Blum *et al.* 1978). In air, it is detectable with a gas-liquid chromatographic analytical procedure (Choudhary 1987).

2.4 Environmental occurrence

DBP is not found naturally in the atmosphere, and most environmental exposures to DBP occur through industrial release. Based on a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere, DBP (with a vapor pressure of 0.09 mm Hg at 25°C) is expected to remain almost entirely in the vapor phase when released into the ambient atmosphere (HSDB 1998). The Toxic Release Inventory (TRI 1996) did not identify DBP as being released by industry into the environment.

2.5 Environmental fate

2.5.1 Air

DBP released into the atmosphere is in vapor form. DBP has an estimated half-life of eight days in the vapor phase of the atmosphere, as a result of reaction with photochemically produced hydroxyl radicals. The estimated eight-day half-life is based on the assumption that the atmospheric concentration of hydroxyl radicals is $5x10^5$ (HSDB 1998).

2.5.2 Water

DBP is not expected to adsorb to suspended solids and sediments in water, and volatilization is not expected to be an important process of elimination from water. The estimated bioconcentration factor (BCF) for DBP is 3; it s potential for bioconcentration is extremely low, because a BCF greater than 1,000 is required for significant

bioaccumulation in aquatic organisms. The volatilization half-life of DBP in a model river (1 m deep, flowing 1 m/sec, and wind velocity of 3 m/sec) is estimated at 107 days. The volatilization half-life of DBP in a model lake (1 m deep, flowing 0.05 m/sec, and wind velocity of 0.5 m/sec) is estimated at 780 days (HSDB 1998).

2.5.3 Soil

Based on a classification scheme by Swann *et al.* (1983, cited in HSDB 1998) and an estimated K_{oc} value of 4, determined via a structure estimation method, DBP is expected to have very high mobility in soil. Volatilization is not expected to be an important process of elimination for DBP in wet or dry soils. In addition, limited data show that DBP may biodegrade under aerobic conditions (HSDB 1998).

2.6 Environmental exposure

The primary modes of potential human exposure to DBP are inhalation and dermal contact. Over 50 million children wearing TRIS-BP-treated sleepwear may have been exposed to DBP (as a metabolite of TRIS-BP) before the 1977 Consumer Product Safety Commission banned the use of TRIS-BP in children's clothing (Blum *et al.* 1978). No consumer exposure or manufacture information was found for DBP.

2.7 Occupational exposure

Occupational exposure to DBP may occur through inhalation and dermal contact in those industries where DBP is used as an intermediate for the production of flame-retardant materials, pharmaceuticals, insecticides, and TRIS-BP. Information on estimated occupational exposures to DBP is not available (HSDB 1998).

2.8 Biological indices of exposure

DBP was found in urine samples from 10 children who were wearing TRIS-BP-treated sleepwear. By mass spectrometry, urine levels were found to range from 0.4 to 29 ng/mL. Low values come from children who were wearing previously washed pajamas, and higher values came from children wearing new, unwashed pajamas. Washing, however, was not considered to diminish the risk of DBP exposure, because guidelines at the time required sleepwear to be flame-resistant for more than 50 washes (Blum *et al.* 1978).

2.9 Regulations

U.S. EPA regulates DBP under the Toxic Substances Control Act (TSCA), requiring manufacturers and processors to report production, use, and any exposure-related information for chemicals with toxic or dangerous characteristics. These regulations are summarized in Table 2-1. No FDA or OSHA regulations were found for DBP and TRIS-BP.

Table 2-1. U.S. EPA regulations

U.S. EPA Regulations	
Regulatory action	Effect of regulation and other comments
40 CFR 712 – PART 712–CHEMICAL INFORMATION RULES. Promulgated: 47 FR 26998, 06/22/82. U.S. Codes: 15 U.S.C. 2607(a). 2,3-Dibromo-1-propanol has an effective date of 10/29/90 and a sunset date of 12/27/90.	This part establishes procedures for chemical manufacturers and processors to report production, use, and exposure-related information on listed chemical substances. Subpart A establishes requirements that apply to all reporting under this part. Subpart B covers manufacturers' and processors' reporting.
40 CFR 716–PART 716–HEALTH AND SAFETY DATA REPORTING. Promulgated: 51 FR 32726, 09/15/86. U.S. Codes: 15 U.S.C. 2607(d). 2,3-Dibromo-1-propanol has an effective date of 10/29/90 and a sunset date of 12/27/95.	The provisions of this part require the submission of lists and copies of health and safety studies on chemical substances and mixtures selected for priority consideration for testing rules under section 4(a) of TSCA and on other chemicals for which U.S. EPA requires health and safety information in fulfilling the purposes of TSCA.

Source: These regulations have been updated through the 1998 Code of Federal Regulations 40 CFR, July 1, 1998.

3 Human Cancer Studies

No case reports or epidemiological studies of the occurrence of human cancer and exposure to 2,3-dibromo-1-propanol were found.

4 Studies of Cancer in Experimental Animals

4.1 Carcinogenesis studies of DBP

4.1.1 Carcinogenicity study in rats

The carcinogenic potential of dermally applied DBP (98% pure) was assessed in male and female F344/N rats (NTP 1993; Eustis *et al.* 1995). Dose levels for the long-term study were selected on the basis of the results of a 13-week range-finding study during which groups of 10 animals of each sex received five applications per week of 0, 44, 88, 177, 375, or 750-mg/kg of DBP dissolved in 95% ethanol. Doses were applied to the shaved interscapular skin five days/week for 13 weeks. After 13 weeks, male rats in the 375-, and 750-mg/kg groups exhibited nephropathy, and female rats in the 750-mg/kg group exhibited hepatocellular necrosis.

In the long-term carcinogenicity study, groups of rats (50/sex) received daily dermal applications of 0, 188, or 375 mg/kg of DBP five days per week. The study was originally planned to last for 104 weeks. The study was terminated, however, at 48 to 51 weeks for males and 52 to 55 weeks for females because of reduced survival in high-dose groups. Early deaths and sacrifices of moribund animals were attributable to treatment-associated neoplasms. Dermal application of DBP caused a variety of dermal and systemic neoplasms in both sexes. Tumor incidences are summarized in Tables 4-1, 4-2, 4-3, and 4-4 (NTP 1993).

Table 4-1. Incidences of skin neoplasms in F344/N rats dosed with DBP for 48 to 55 weeks

Tumor type	Daily dose (mg/kg)		
	0	188	375
	Tumor incidence/number examined[a]		
Males			
Squamous cell papilloma	1/50	3/50	0/50
Squamous cell carcinoma	0/50	5/50*	8/50**
Basal cell tumor	0/50	13/50**	21/50**
Sebaceous adenoma	0/50	5/50*	5/50*
Keratoacanthoma	0/50	4/50	12/50**
Neoplasms, any type	1/50	22/50**	33/50**
Females			
Squamous cell papilloma	0/50	0/50	2/50
Squamous cell carcinoma	0/50	0/50	1/50
Basal cell tumor	0/50	3/50	12/50**
Sebaceous adenoma	0/50	0/50	2/50
Keratoacanthoma	0/50	0/50	5/50*
Neoplasms, any type	0/50	3/50	18/50**

Source: NTP (1993).

[a]Statistically significant by Fisher exact test: *$P \leq 0.05$; **$P \leq 0.01$

Table 4-2. Incidences of digestive tract neoplasms in F344/N rats dosed with DBP for 48 to 55 weeks

Tumor type	Daily dose (mg/kg)		
	0	188	375
	Tumor incidence/number examined[a]		
Males			
Oral mucosa			
Squamous cell papilloma	0/50	40/50*	33/50*
Squamous cell carcinoma	0/50	16/50*	25/50*
Esophagus			
Squamous cell papilloma	0/50	19/50*	33/50*
Squamous cell carcinoma	0/50	1/50	0/50
Forestomach			
Squamous cell papilloma	0/50	1/50	17/50*
Small intestine			
Adenomatous polyp	0/50	1/50	3/50
Adenocarcinoma	0/50	8/50*	11/50*
Large intestine			
Adenomatous polyp	1/50	13/50*	29/50*
Adenocarcinoma	1/50	1/50	2/50
Females			
Oral mucosa			
Squamous cell papilloma	0/50	27/50*	41/50*
Squamous cell carcinoma	0/50	15/50*	27/50*
Esophagus			
Squamous cell papilloma	0/50	9/50*	38/50*
Squamous cell carcinoma	0/50	0/50	1/50
Forestomach			
Squamous cell papilloma	1/50	3/50	23/50*
Small intestine			
Adenomatous polyp	0/50	1/50	0/49
Adenocarcinoma	0/50	3/50	4/49
Large intestine			
Adenomatous polyp	0/50	12/50*	37/50*
Adenocarcinoma	0/50	0/50	0/50

Source: NTP (1993).

[a]Statistically significant by Fisher exact test: *$P \leq 0.001$.

Table 4-3. Incidences of neoplastic and nonneoplastic lesions of the nasal mucosa, Zymbal gland, liver, and kidney in F344/N rats dosed for 48 to 55 weeks with DBP

Tumor type	Daily dose (mg/kg)		
	0	188	375
	Tumor incidence/number examined[a]		
Males			
Nasal mucosa			
Adenoma	0/50	48/50**	48/50**
Adenocarcinoma	0/50	2/50	1/50
Zymbal gland			
Adenoma	0/50	1/50	7/50*
Adenocarcinoma	0/50	8/50*	29/50**
Liver			
Neoplastic nodule	0/49	3/50	2/50
Carcinoma	0/49	1/50	3/50
Kidney			
Adenoma	0/50	0/50	4/50
Females			
Nasal mucosa			
Adenoma	1/50	44/50**	49/50**
Zymbal gland			
Adenoma	0/50	7/50*	3/50
Adenocarcinoma	1/50	2/50	19/50**
Liver			
Neoplastic nodule	0/50	10/50**	11/50**
Carcinoma	0/50	2/50	6/50*
Kidney			
Adenoma	0/50	1/50	4/50

Source: NTP (1993).

[a]Statistically significant by Fisher exact test: *$P \leq 0.05$; **$P \leq 0.001$.

Table 4-4. Incidences of other neoplasms in Fischer 344/N rats dosed with DBP for 48 to 55 weeks

Tumor type	Daily dose (mg/kg)		
	0	188	375
	Tumor incidence/number examined[a]		
Males			
Peritoneum (tunica vaginalis)			
Mesothelioma	0/50	1/50	4/50
Spleen			
Hemangioma	0/50	0/50	3/50
Hemangiosarcoma	0/50	0/50	1/50
Females			
Clitoral gland			
Adenoma	0/50	1/50	3/50
Adenocarcinoma	0/50	0/50	3/50
Mammary gland			
Adenocarcinoma	0/50	0/50	5/50*

Source: NTP (1993).

[a]Statistically significant by Fisher exact test: *$P \leq 0.05$.

4.1.2 Carcinogenicity study in mice

The carcinogenic potential of dermally applied DBP (98% pure) was assessed in male and female $B6C3F_1$ mice (NTP 1993; Eustis *et al.* 1995). Dose levels for the long-term carcinogenicity study were selected on the basis of the results of a 13-week range-finding study during which groups of 10 animals of each sex received five applications per week of 0, 44, 88, 177, 375, or 750 mg/kg of DBP dissolved in 95% ethanol. Doses were applied to the shaved interscapular skin five days/week for 13 weeks. Dosed mice had treatment-associated bronchiole pleomorphism after administration of DBP at 88, 177, 375 or 750 mg/kg to males or 375 or 750 mg/kg to females. The incidence of centrilobular hepatocellular necrosis also was increased among males in the 750-mg/kg group, and among female in 177-, 375-, or 750-mg/kg groups.

During the long-term carcinogenicity study, groups of 50 male and 50 female mice received daily dermal applications of 0, 88, or 177 mg/kg of DBP five days per week. The planned two-year study was terminated at 36 to 39 weeks for males and 39 to 42 weeks for females because antibodies to lymphocytic choriomeningitis (LCM) virus were detected in sentinel animals housed in the same room. Although LCM depresses humoral and cellular immunity, it is unlikely that the LCM infection affected the outcome of this long-term study as it relates to the carcinogenic potential of DBP. The infection occurred in only 13% of both control and treated mice and the incidence of neoplasms in the control mice was comparable to historical controls. Thus, carcinogenic response was comparable between LCM-infected and LCM-uninfected mice of the same dose group and the induced neoplasms in exposed mice occurred with very high incidences and short

latency (NTP 1993). Despite the study's abbreviated duration, it provides unequivocal evidence of carcinogenicity of DBP in $B6C3F_1$ mice. Dermal application of DBP caused a variety of dermal and forestomach neoplasms in both sexes, pulmonary tumors in both sexes, and liver tumors in males. The incidences of tumors in male and female mice are summarized in Table 4-5.

Table 4-5. Incidences of neoplasms in $B6C3F_1$ mice dosed with DBP for 36 to 42 weeks

Tumor type	Daily dose (mg/kg)		
	0	188	375
	Tumor incidence/number examined[a]		
Males			
Skin			
Squamous cell papilloma	0/50	3/50	9/50**
Squamous cell carcinoma	0/50	0/50	2/50
Sebaceous gland adenoma	0/50	1/50	8/50*
Neoplasms, any type	0/50	4/50	18/50**
Forestomach			
Squamous papilloma	0/50	12/50**	20/49**
Squamous carcinoma	0/50	2/50	1/49
Lung			
Alveolar/bronchiolar adenoma	1/50	1/50	6/50
Alveolar/bronchiolar carcinoma	0/50	0/50	0/50
Liver			
Hepatocellular adenoma	1/50	2/50	9/50*
Hepatocellular carcinoma	0/50	0/50	3/50
Females			
Skin			
Squamous cell papilloma	0/50	1/50	5/50*
Squamous cell carcinoma	0/50	0/50	1/50
Sebaceous gland adenoma	0/50	3/50	2/50
Neoplasms, any type	0/50	4/50	9/50**
Forestomach			
Squamous papilloma	0/50	12/49**	17/50**
Squamous carcinoma	0/50	7/49*	6/50*

Tumor type	Daily dose (mg/kg)		
	0	188	375
	Tumor incidence/number examined[a]		
Lung			
Alveolar/bronchiolar adenoma	0/50	3/50	4/50
Alveolar/bronchiolar carcinoma	1/50	0/50	0/50
Liver			
Hepatocellular adenoma	0/50	0/50	1/50
Hepatocellular carcinoma	1/50	0/50	0/50

Source: NTP (1993).
[a]Statistically significant by Fisher exact test: *$P \leq 0.05$; **$P \leq 0.001$.

4.1.3 Nonneoplastic changes observed during carcinogenesis studies of DBP

In addition to the multiple-organ carcinogenic responses of rats and mice to dermal application of DBP, administration of the chemical caused a variety of nonneoplastic responses. In rats, DBP caused increased incidences of hyperkeratosis in the skin, forestomach, and esophagus; epithelial dysplasia in the nose; pleomorphism and basophilic and clear cell changes in the liver; and nuclear enlargement in the kidney. Other observations included DBP-related increases in the incidences of forestomach ulcers and acanthosis, angiectasis in the liver, and renal hyperplasia in male rats and epithelial dysplasia of the forestomach and bile duct hyperplasia in the liver of female rats (NTP 1993).

In mice, which received DBP for a shorter time than rats, observations included DBP-related hyperplasia in the skin, epithelial dysplasia of the forestomach, and bronchiolar epithelial pleomorphism and hyperplasia in both sexes. The incidence of eosinophilic cytoplasmic change was increased in the livers of male mice (NTP 1993).

4.2 Studies with TRIS-BP

DBP is a metabolite of the flame retardant, TRIS-BP. Dietary administration of TRIS-BP to Fischer 344 rats (50 or 100 ppm) and B6C3F_1 mice (500 or 1000 ppm) for 103 weeks caused multiple organ carcinogenesis in both sexes of both species. In male and female rats, TRIS-BP administration was associated with significantly increased incidences of tubular cell neoplasms of the kidney. TRIS-BP-dosed mice exhibited increased incidences of neoplasms of the forestomach and lung in both male and female mice, kidney in male mice, and liver in female mice (NCI 1978, cited in IARC 1979, NTP 1993; Reznik *et al.* 1979, cited in NTP 1993). In another study, the dermal application of 10 or 30 mg of TRIS-BP three times a week for 67 to 71 weeks to the dorsal skin of ICR/Ha Swiss mice resulted in increased incidences of neoplasm of the skin, forestomach, oral cavity, and lung (Van Duuren *et al.* 1978, cited in IARC 1979, NTP 1993). A third study observed adenomas of the colon in F344/N rats administered gavage doses of 100 mg/kg TRIS-BP in corn oil, five days a week for 52 weeks (Reznik *et al.* 1981, cited in IARC 1999; NTP 1993).

Based on these observations, the IARC considers TRIS-BP to be *probably carcinogenic to humans* (*Group 2A*) (IARC 1999) and the NTP considers TRIS-BP to be *reasonably anticipated to be a human carcinogen* (NTP 1993).

4.3 Summary

DBP is carcinogenic to both sexes of rats and mice, causing increased incidences of benign and malignant tumors in multiple organs.

5 Genotoxicity

5.1 Prokaryotic systems

5.1.1 Induction of mutation in Salmonella typhimurium

DBP was mutagenic in *Salmonella typhimurium* strain TA100 both when incubated at a concentration of 0.05 mM with metabolic activation by S9 liver homogenate from phenobarbital-treated rats and when co-cultured with hepatocytes isolated from untreated rats (Holme *et al*. 1983).

NTP (1993) tested DBP for mutagenicity in various strains of *S. typhimurium. In vitro* assays were conducted in *S. typhimurium* strains TA100, TA1535, TA1537, and TA98 at DBP concentrations ranging from 0.0 to 2000.0 μg/plate in the presence or absence of a 10% hamster or rat S9 metabolic activating system. DBP was mutagenic in *S. typhimurium* strains TA100, TA1535, and TA98 in the presence or absence of hamster or rat S9 metabolic activation. In strain TA1537, DBP was nonmutagenic without S9 activation or with hamster S9 metabolic activation, and gave equivocal results with rat S9 metabolic activation. The highest concentration of DBP tested (2000 μg/plate) was toxic to *S. typhimurium* strains TA1537 and TA98. At 1,000 μg/plate, DBP was slightly toxic to all *S. typhimurium* strains tested.

DBP gave positive results in assays conducted to evaluate its oxidative and crosslinking potential. In these assays, DBP was tested in *S. typhimurium* strains TA102 (*his*G428, *rfa*, pKM101) and TA2638 (*hisG428*, *rfa*, pKM101) at concentrations ranging from 0 to 5,000 μg/plate, by the plate incorporation method, in the presence or absence of liver S9 metabolic activation. Both strains TA102 and TA2638 are sensitive in the detection of oxidative agents and crosslinking agents, because they contain AT base pairs at the hotspot (*his*G428) (Watanabe *et al*. 1998).

5.1.2 Induction of mutation in Escherichia coli

The mutagenicity of DBP was evaluated in two *Escherichia coli* strains, WP2/pKM101 (*trpE*56, pKM101) and WP2 uvrA/pKM101 (*trpE*56, *uvra*, pKM101), sensitive in detecting oxidative agents and crosslinking agents. DBP was tested at concentrations ranging from 0 to 5,000 μg/plate, by the plate incorporation method, in the presence or absence of liver S9 metabolic activation. DBP was mutagenic with or without activation in both strains, although the WP2 *uvr*A/pKM10 strain of *E. coli* was more sensitive in detecting mutations induced by oxidative and crosslinking agents. DBP was toxic to both *E. coli* strains at the highest concentration tested (Watanabe *et al*. 1998).

5.2 Eukaryotic systems

5.2.1 Mutagenicity in Drosophila melanogaster

5.2.1.1 Sex-linked recessive lethal assay

DBP caused sex-linked recessive lethal mutations in the germ cells of *Drosophila melanogaster* in three mating trails when adult males received DBP at a concentration of 500 ppm in feed. In three mating trials, 51% of flies died and 9% became sterile. A

combined total of 53 lethal mutations per three broods tested was observed (Yoon *et al*. 1985, cited in NTP 1993).

5.2.1.2 Reciprocal translocation test

When administered to adult *D. melanogaster* in feed at a concentration of 400 ppm, DBP induced a significant increase in reciprocal translocations ($P < 0.01$). The increase in frequency of reciprocal translocations was 36-fold relative to concurrent controls and 18-fold relative to historical controls (Yoon *et al*. 1985, cited in NTP 1993).

The recombinagenic potential of DBP was tested in another study using the *D. melanogaster* w/w+ eye mosaic assay, an *in vivo* short-term test measuring genetic damage in somatic cells of *Drosophila* after treatment of larvae. DBP was clearly recombinagenic at concentrations of 0.10 and 0.25 nM under the conditions of this assay (Vogel and Nivard 1993).

5.3 Mammalian Systems

5.3.1 In vitro *assays*

5.3.1.1 Mouse lymphoma assay

DBP was tested for its potential to induce trifluorothymidine resistance in L5178Y mouse lymphoma cells at concentrations ranging from 0.0625 to 0.75 μg/mL in two trials without metabolic activation (NTP 1993). In the first trial, DBP significantly increased induction of trifluorothymidine resistance at a concentration of ≥ 0.125 μg/mL, with an average mutation frequency of 69%. In the second trial, DBP significantly increased the induction of trifluorothymidine resistance at a concentration of ≥ 0.0625 μg/mL, with an average mutation frequency of 88%. The highest concentration (0.75 μg/mL) was lethal to the mouse lymphoma cells.

DBP was mutagenic in Chinese hamster V79 lung cells at a concentration of 0.02 mM with metabolic activation by S9 liver homogenate from phenobarbital-treated rats. The number of 6-thioguanine-resistant mutants was increased by a factor of 4.5 (15.8 mutations/10^6 cells, compared with 3.5 mutations/10^6 cells in dimethylsulfoxide controls) (Holme *et al*. 1983).

5.3.1.2 Sister chromatid exchanges and chromosomal aberrations

Increases in sister chromatid exchanges (SCE) were observed when DBP was incubated with Chinese hamster ovary (CHO) cells at concentrations ranging from 50.9 to 1,700.0 μg/mL with or without metabolic activation by S9 liver homogenate from Aroclor 1254-induced male Sprague-Dawley rats (NTP 1993). DBP induced SCE (20% increase over solvent control, $P < 0.001$) in a concentration-dependent manner at DBP concentrations up to 508.80 μg/mL with or without activation. DBP also was tested at concentrations ranging from 110.7 to 507.1 μg/mL without S9 metabolic activation. DBP induced SCE in a concentration-dependent manner at concentrations up to 253.6 μg/mL.

In a test of its potential to induce chromosomal aberrations, DBP was incubated with CHO cells at concentrations ranging from 626.4 to 2,493.1 μg/mL with or without

metabolic activation by S9 liver homogenate from Aroclor 1254-induced male Sprague-Dawley rats (NTP 1993). Chromosomal aberrations were significantly increased ($P < 0.001$) at concentrations up to 1,869.8 µg/mL with or without metabolic activation. DBP also was tested at concentrations ranging from 620.6 to 2,238.7 µg/mL without S9 metabolic activation. Chromosomal aberrations were significantly increased at concentrations up to 1,880.5 µg/mL.

5.3.2 In vivo *assays*

5.3.2.1 Mouse bone marrow micronucleus test

In a test of DBP's potential to induce micronuclei *in vivo*, male $B6C3F_1$ mice were given 0, 25, 50, or 100 mg/kg DBP by intraperitoneal injection, three times over a 24-hour period. DBP failed to increase the frequency of micronucleated cells ($P = 0.763$) or of polychromatic micronucleated erythrocytes ($P = 0.363$) in the bone marrow of mice. DBP was nontoxic to bone marrow over the dose range tested (NTP 1993).

5.4 Summary

DBP is a direct-acting mutagen, causing gene mutation in *S. typhimurium* with or without metabolic activation and inducing sex-linked recessive lethal mutations and reciprocal translocations in *D. melanogaster*.

6 Other Relevant Data

6.1 Absorption of DBP

Dermal absorption of DBP was measured in male Fischer 344/N rats (six weeks old) and male $B6C3F_1$ mice (eight weeks old) and blood concentrations following dermal and oral (gavage) exposure were compared (NTP 1993).

Animals were fasted (rats, overnight; mice, four hours) before dermal or gavage administration of DBP. For dermal application, DBP was dissolved in ethanol; for gavage administration, it was mixed with corn oil. Twenty-eight rats received 500 mg/kg of DBP and 28 mice received 177 mg/kg of DBP applied to their shaved interscapular skin. Twenty-eight rats and 28 mice received 177 mg/kg of DBP by gavage. The concentration of DBP in blood was determined at 0.25, 0.5, 1, 2, 4, 12, and 24 hours after dosing. Blood was analyzed by a gas chromatography method. The results are summarized in Tables 6-1 and 6-2 (NTP 1993).

Table 6-1. Concentration of DBP (10^{-7} g/mL) in the blood of rats following gavage or dermal administration

Time after dosing (h)	Gavage		Dermal	
	Vehicle Control[a]	177 mg/kg[b]	Vehicle Control[a]	500 mg/kg[b]
0.25	1.0	65.6 ± 14.7	21.6	126.2 ± 29.9
0.5	2.6	47.2 ± 27.4	2.6	45.3 ± 17.7
1	1.9	10.3 ± 2.5	1.5	116.6 ± 37.1
2	4.9	10.0 ± 2.7	4.9	8.1 ± 1.3
4	2.8	6.6 ± 2.2	2.4	2.0 ± 0.3
12	0.9	7.5 ± 3.5	1.3	1.5 ± 0.3
24	0.5	6.5 ± 2.7[c]	1.3	1.3 ± 0.4

Source: NTP (1993)
[a] Results of triplicate analyses of samples taken from a single vehicle control animal per time period.
[b] Mean ± SE for groups of four animals unless otherwise specified. Results of triplicate analyses.
[c] N=3

Table 6-2. Concentration of DBP (10^{-7} g/mL) in the blood of mice following gavage or dermal administration

Time after dosing (h)	Gavage		Dermal	
	Vehicle Control[a]	177 mg/kg[b]	Vehicle Control	177 mg/kg[b]
0.25	1.7	21.3 ± 3.1	2.1	17.9 ± 2.2
0.5	1.3	35.2 ± 7.3	1.6	19.1 ± 4.7
1	0.7	19.4 ± 8.4	0.6	4.8 ± 1.1
2	0.9	51.6 ± 15.1	1.2	1.8 ± 0.4
4	1.0	19.7 ± 5.5	0.9	0.9 ± 0.3
12	0.5	2.2 ± 0.5	0.6	0.6 ± 0.1
24	1.5	1.6 ± 0.4	2.2	1.2 ± 0.3

Source: NTP (1993)
[a] Results of triplicate analyses of samples taken from a single vehicle control animal per time period.
[b] Mean ± SE for groups of four animals. Results of triplicate analyses.

DBP was absorbed rapidly and extensively after either dermal or oral administration. The highest concentrations of DBP in blood were found 15 minutes after dermal or gavage administration in rats and 30 minutes after dermal administration or 2 hours after gavage administration in mice. The efficiency of dermal absorption, relative to oral absorption was estimated to be 68% for rats and 37% for mice. The chemical was consistently cleared from blood in less than 4 hours, except in the case of gavage administration in mice, where clearance was complete in less than 12 hours.

6.2 Metabolism of DBP

DBP is a metabolite of TRIS-BP. Current understanding of the metabolism of DBP stems from studies of metabolism of the parent compound. The probable metabolism of DBP was reviewed by NTP (1993) and is shown in Figure 6-1.

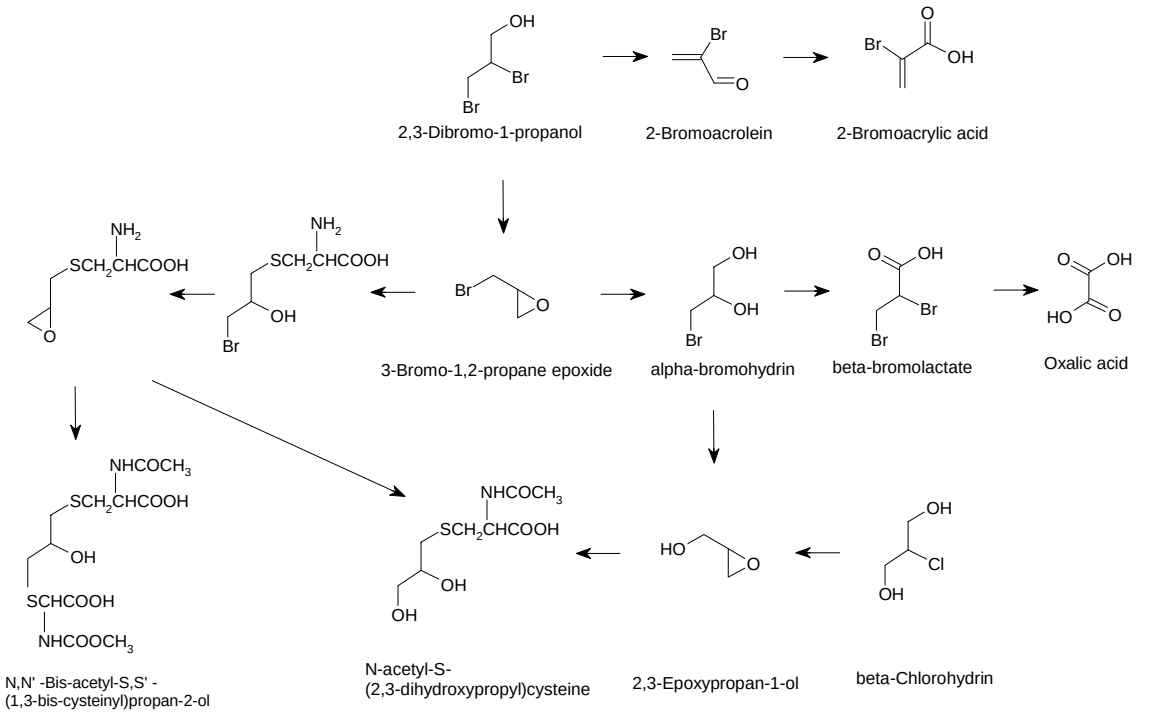

Figure 6-1. Proposed metabolic pathway for DBP

Source: Jones and Fakhouri (1979), Marsden and Casida (1982), both cited in NTP (1993).

Marsden and Casida (1982, cited in NTP 1993) suggested that DBP undergoes oxidation and dehydrohalogenation to form an unstable intermediate, 2-bromoacrolein, which results in the formation of 2-bromoacrylic acid. The researchers identified haloacrylic acids in the urine of rats administered either dibromo- or dichloro-propanol.

DBP also may undergo oxidation to 3-bromo-1,2-propane epoxide, which may react with glutathione to form *N*,*N*′-bis-acetyl-*S*,*S*′-(1,3-bis-cysteinyl)propan-2-ol and *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine. Both of these thio metabolites have been identified in the urine of rats administered dihalopropanols (Jones and Fakhouri 1979, cited in NTP 1993). These investigators also identified β-bromolactate in the urine of rats given DBP. This observation suggests that, in addition to conjugation with glutathione, 3-bromo-1,2-propane epoxide may also undergo hydrolysis to form α-bromohydrin which is then oxidized to form β-bromolactate.

Jones and Fakhouri (1979, cited in NTP 1993) also reported that when β-chlorohydrin was administered to rats, it resulted in the formation of *N*-acetyl-*S*-(2,3-dihydroxypropyl)cysteine. The same metabolite was found in the urine of rats dosed with α-chlorohydrin (Jones 1973, cited in NTP 1993). In order for the metabolite to be produced from α- and β-chlorohydrin, they both must be converted to the epoxide, 2,3-epoxypropan-1-ol. This observation was considered additional evidence of the obligatory formation of epoxides as intermediate metabolites during the metabolism of DBP (NTP 1993).

6.3 Genotoxicity of putative metabolites of DBP

DBP is mutagenic in *Salmonella typhimurium* strains TA98, TA100, and TA1535 (see Section 5.1.1), and its mutagenic activity is enhanced by the presence of metabolic activating systems. 2-Bromoacrolein, identified in the urine of rats dosed with TRIS-BP and a probable reactive metabolite of DBP, is mutagenic in *S. typhimurium* strain TA100 with and without metabolic activation. This metabolite also causes DNA damage in cultured hepatoma cells and induces morphological transformation of Syrian hamster embryo cells (Gordon *et al*. 1985).

6.4 Metabolism of TRIS-BP to DBP

DBP is a metabolite of TRIS-BP in humans. DBP was detected in the urine of a seven year old female child who wore TRIS-BP-treated sleepwear for 12 consecutive nights. Urinary DBP concentrations ranged from 0.4 to 29 ng/mL (Blum *et al.* 1978).

In animal studies, DBP was identified among the urinary and biliary products in rats were intravenously and orally administered TRIS-BP. Urinary hydrolysis products, free and conjugated forms of DBP, also were found in rats administered 100 mg of TRIS by dermal application (St. John *et al.* 1976, cited in IARC 1979). *In vitro*, DBP is formed following addition of reduced nicotinamide adenine dinucleotide-dependent microsomal enzymes from rat liver to TRIS-BP (Nomeir and Matthews 1983).

6.5 Summary

DBP is readily absorbed from the gastrointestinal tract and through intact skin of rats and mice. In humans and rats, TRIS-BP is metabolized to DBP. Indirect evidence, largely generated during studies of the metabolism of the carcinogenic flame retardant TRIS-BP, indicates that DBP undergoes biotransformation in rats. The putative metabolic pathways probably produce at least three epoxide intermediates. DBP *per se* has been shown to be a mutagen, and its mutagenic activity is enhanced by the presence of hepatic microsomal metabolizing systems.

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