TRIS(2,3-DIBROMOPROPYL) PHOSPHATE

Data were last reviewed in IARC (1979) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

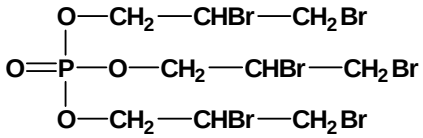
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 126-72-7
Chem. Abstr. Name: 2,3-Dibromo-1-propanol phosphate (3:1)
IUPAC Systematic Name: 2,3-Dibromo-1-propanol phosphate
Synonyms: Phosphoric acid, tris(2,3-dibromopropyl) ester; Tris

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_9H_{15}Br_6O_4P$ Relative molecular mass: 697.61

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Viscous liquid (Budavari, 1996)
(*b*) *Boiling-point*: 390°C (WHO, 1995)
(*c*) *Melting-point*: 5.5°C (WHO, 1995)
(*d*) *Solubility*: Slightly soluble in water (0.8 mg/L at 24°C); miscible with carbon tetrachloride, chloroform and dichloromethane (Verschueren, 1996; United States National Library of Medicine, 1997)
(*e*) *Vapour pressure*: 0.03 Pa at 25°C (WHO, 1995)
(*f*) *Octanol/water partition coefficient (P)*: log *P*, 3.02 (WHO, 1995)
(*g*) *Conversion factor*: $mg/m^3 = 28.54 \times ppm$

1.2 Production and use

Production of tris(2,3-dibromopropyl) phosphate in the United States in 1975 was estimated to be between 4100 and 5400 tonnes. There are no reports of current production anywhere other than for research purposes (WHO, 1995).

Tris(2,3-dibromopropyl) phosphate has been used as a flame retardant for plastics and in synthetic textiles and fibres, which have been fabricated into children's clothing (Lewis, 1993).

1.3 Occurrence

1.3.1 *Occupational exposure*

Occupational exposures to tris(2,3-dibromopropyl) phosphate may have occurred during its production in the textile and polyurethane foam industries (IARC, 1979).

1.3.2 *Environmental occurrence*

Environmental release in the past has been shown to result from textile finishing plants and laundering of the finished product (United States National Library of Medicine, 1997).

Tris(2,3-dibromopropyl) phosphate was found in the air and soil in the United States in the 1970s. None was found in samples taken from various water and soil sources in Japan at this time. General population exposures may have occurred from the use of clothing treated with the compound (WHO, 1995).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has not proposed any occupational exposure limit for tris(2,3-dibromopropyl) phosphate. Finland, Sweden and France have a carcinogen notation (United States National Library of Medicine, 1997).

No international guideline for tris(2,3-dibromopropyl) phosphate in drinking-water has been established (WHO, 1993).

2. Studies of Cancer in Humans

In a cohort mortality study in the United States, a group of 628 male workers was classified as exposed to tris(2,3-dibromopropyl) phosphate either on a 'routine' or 'non-routine' basis; 36 deaths occurred in this group (35 expected), seven of which were due to cancer compared with 6.6 that would have been expected (Wong *et al.*, 1984).

3. Studies of Cancer in Experimental Animals

Tris(2,3-dibromopropyl) phosphate was tested for carcinogenicity in one experiment in mice and in one in rats by oral administration and in one experiment in female mice by skin application. In mice, following oral administration, it produced benign and malignant tumours of the forestomach and lung in animals of both sexes, benign and malignant liver tumours in females and benign and malignant tumours of the kidney

(of the tubule cells) in males. In rats, it produced benign and malignant tumours of the kidney (of the tubule cells) in males and benign kidney tumours (of the tubule cells) in females. After skin application to female mice, it produced tumours of the skin, lung, forestomach and oral cavity (IARC, 1979).

3.1 Oral administration

Rat: A group of 50 male Fischer 344 rats, four weeks of age, was administered 100 mg/kg bw tris(2,3-dibromopropyl) phosphate [purity unspecified] dissolved in vegetable oil by gavage on five days per week for four weeks. After four weeks, the group was divided into three subgroups of 20, 15 and 15 rats. The first group received no further exposure; in the second subgroup, tris(2,3-dibromopropyl) phosphate administration was continued for 48 weeks; the third subgroup received vegetable oil (vehicle) alone for the remainder of the experiment. Two control groups consisted of 27 rats treated with vegetable oil (vehicle) alone and seven rats which received no treatment. The study was terminated at 52 weeks. Rats were killed at various time intervals to study the reversibility of tris(2,3-dibromopropyl) phosphate-induced lesions. In the rats treated for 52 weeks with tris(2,3-dibromopropyl) phosphate, one developed a kidney adenocarcinoma and 3/5 rats surviving at 52 weeks had adenomas of the descending colon (Reznik *et al*., 1981). [The Working Group noted the short duration of the experiment.]

3.2 Carcinogenicity of metabolites

3.2.1 *2,3-Dibromo-1-propanol*

Mouse: Groups of 50 male and 50 female B6C3F_1 mice, eight weeks of age, were administered skin applications of 0, 88 or 177 mg/kg bw 2,3-dibromo-1-propanol (98% pure) in 95% ethanol on five days per week for 36–39 weeks (males) or 39–42 weeks (females). The study was terminated at 36–39 weeks (males) and 39–42 weeks (females) because sera from sentinel mice housed in the same room as the study animals were found to be positive for antibodies to lymphocytic choriomeningitis virus. As shown in Table 1, increased incidences of skin papillomas, forestomach papillomas and forestomach carcinomas were observed in both sexes. Hepatocellular adenomas were seen in 1/50 control, 2/50 low-dose and 9/50 high-dose ($p < 0.05$) male mice; no data for liver were reported in females (Eustis *et al*., 1995).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, eight weeks of age, were administered skin applications of 0, 188 or 375 mg/kg bw 2,3-dibromo-1-propanol (98% pure) in 95% ethanol on five days per week for 48–51 weeks (males) or 52–55 weeks (females). The study was terminated at 48–51 weeks for males and 52–55 weeks for females because of reduced survival of the high-dose groups and because sentinel mice housed in the same room as the rats tested positive for lymphocytic choriomeningitis virus. As shown in Table 2, there were increased incidences of skin neoplasms (all types), squamous-cell carcinomas of the skin, basal-cell tumours [not further specified] of the skin, squamous-cell carcinomas of the oral mucosa, squamous-cell papillomas of the oesophagus, squamous-cell papillomas of the forestomach, adenocarcinomas of the

Table 1. Increased tumour incidences in mice administered 2,3-dibromo-1-propanol by skin application

Tumour type	Controls		Low dose		High dose	
	Males	Females	Males	Females	Males	Females
Skin papillomas	0/50	0/50	3/50	1/50	9/50**	5/50*
Forestomach papillomas	0/50	0/50	12/50**	12/49**	20/49**	17/50**
Forestomach carcinomas	0/50	0/50	2/50	7/49**	1/49	6/50*

*$p < 0.05$
**$p < 0.01$
From Eustis *et al.* (1995)

Table 2. Increased tumour incidences in rats administered 2,3-dibromo-1-propanol by skin application

Tumour type	Controls		Low dose		High dose	
	Males	Females	Males	Females	Males	Females
Skin (all types)	1/50	0/50	22/50**	3/50	33/50**	18/50**
Skin, squamous-cell carcinomas	0/50	0/50	5/50*	0/50	8/50**	1/50
Skin, basal cell tumours	0/50	0/50	13/50**	3/50	21/50**	12/50**
Oral mucosa, squamous-cell carcinomas	0/50	0/50	16/50**	15/50**	25/50**	27/50**
Oesophagus, squamous-cell papillomas	0/50	0/50	19/50**	9/50	33/50**	38/50
Stomach, squamous-cell papillomas	0/50	1/50	1/50	3/50	17/50**	23/50**
Small intestine, adenocarcinomas	0/50	0/50	8/50**	3/50	11/50**	4/50
Large intestine, adenomatous polyps	1/50	0/50	13/50**	12/50**	29/50**	37/50**
Nasal mucosa, adenomas	0/50	0/50	48/50**	44/50**	48/50**	49/50**
Zymbal gland, adenocarcinomas	0/50	1/50	8/50**	2/50	29/50**	19/50**
Liver, carcinomas	0/50	0/50	1/50	2/50	3/50	6/50*

*$p < 0.05$
**$p < 0.01$
From Eustis *et al.* (1995)

small intestine, adenomatous polyps of the large intestine, adenomas of the nasal mucosa, Zymbal gland adenocarcinomas and liver carcinomas (Eustis *et al*., 1995).

3.2.2 *Bis(2,3-dibromopropyl) phosphate*

Rat: Groups of 40 male and 40 female Wistar rats, five weeks of age, were administered the magnesium salt of bis(2,3-dibromopropyl) phosphate [purity not specified] mixed in the diet at concentrations of 0 (control), 80 (low-dose), 400 (mid-dose) or 2000 (high-dose) mg/kg diet (ppm) for 24 months. Oesophageal papillomas were observed in 0/40 control, 0/40 low-dose, 6/40 mid-dose ($p < 0.05$) and 2/40 high-dose males and in 0/40 control, 0/40 low-dose, 0/40 mid-dose and 6/40 high-dose ($p < 0.05$) females. Papillomas of the forestomach were seen in 0/40 control, 0/40 low-dose, 8/40 mid-dose ($p < 0.05$) and 17/40 high-dose ($p < 0.01$) males and in 0/40 control, 0/40 low-dose, 4/40 mid-dose and 20/40 high-dose ($p < 0.01$) females. Adenocarcinomas of the small intestine were observed in 0/40 control, 0/40 low-dose, 2/40 mid-dose and 14/40 high-dose ($p < 0.01$) males and in 0/40 control, 0/40 low-dose, 0/40 mid-dose and 9/40 high-dose ($p < 0.01$) females. Hepatocellular carcinomas were observed in 0/40 control, 1/40 low-dose, 7/40 mid-dose ($p < 0.05$) and 24/40 high-dose ($p < 0.01$) female rats (Takada *et al*., 1991).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

The excretion balance and tissue distribution of radiolabelled tris(2,3-dibromopropyl) phosphate in rats were examined by Lynn *et al*. (1980, 1982) and Nomeir and Matthews (1983). After intravenous administration of 1.76 mg/rat, Lynn *et al*. (1980) recovered 57% of the dose in the urine in five days and identified the diester bis(2,3-dibromopropyl) phosphate as a minor urinary metabolite (7.8% of urinary ^{14}C). In further work, Lynn *et al*. (1982) recovered a total of 86% of the dose in the excreta (58% urine, 9% faeces, 19% as expired $^{14}CO_2$) with a further 9% in the carcass. Bile-duct-cannulated rats excreted 34% of the dose in the bile in 24 h, 20% being eliminated in the first hour after dosing. No unchanged tris(2,3-dibromopropyl) phosphate was detected in the urine, but dibromopropanol was present in addition to the diester previously reported. On high-performance liquid chromatography, numerous ^{14}C peaks remained unidentified.

Nomeir and Matthews (1983) compared the disposition of tris(2,3-dibromo[1-^{14}C]-propyl) phosphate given intravenously and orally to rats at a dose of 1.4 mg/kg bw (2 μmol/kg bw). Absorption from the gastrointestinal tract was extensive and rapid, the

tissue levels of ^{14}C being essentially identical after both routes of administration. After 24 h, 24% of an oral dose and 17% of an intravenous dose were present in urine and 11% (oral dose), 7% (intravenous dose) in faeces, with 21% (oral dose) and 26% (intravenous dose) present in seven tissues examined. A further 20% was recovered as exhaled $^{14}CO_2$ after intravenous dosing; no data were reported on exhalation after oral dosing. The tissue distribution of ^{14}C was widespread, with an elimination half-life of 60 h from most tissues and 91 h from liver and kidney.

Lynn *et al.* (1982) detected three major ^{14}C-containing compounds in plasma and the pattern was dominated by bis(2,3-dibromopropyl) phosphate as early as 5 min after intravenous dosing. 2,3-Dibromopropanol was also detected up to 8 h after dosing. The elimination of bis(2,3-dibromopropyl) phosphate was biphasic, with half-lives of 6 and 36 h and it was detected up to five days after dosing.

Tissue distribution was examined at five time points, with separate determinations of total ^{14}C, tris(2,3-dibromopropyl) phosphate and bis(2,3,-dibromopropyl) phosphate. The results confirmed the rapid disappearance of tris(2,3-dibromopropyl) phosphate, this being detected only at 5 and 30 min. Bis(2,3-dibromopropyl) phosphate was the major component in blood, lung, muscle and fat and had a long elimination period. At five days after dosing, there was significant retention of ^{14}C in the kidney, this comprising various polar components with some bis(2,3-dibromopropyl) phosphate also detected. The extensive biliary excretion of tris(2,3-dibromopropyl) phosphate-related radioactivity and low faecal elimination of the radiolabel indicate that enterohepatic circulation contributes to the retention of ^{14}C in the body (Lynn *et al.*, 1982).

In addition to the previously reported bis(2,3-dibromopropyl) phosphate and 2,3-dibromopropanol, Nomeir and Matthews (1983) characterized four additional metabolites by mass spectrometry, that arose from further hydrolysis and dehydrobromination of the 2,3-dibromopropane moiety, namely 2-bromo-2-propenyl-2,3-dibromopropyl phosphate, bis(2-bromo-2-propenyl) phosphate, 2,3-dibromopropyl phosphate and 2-bromo-2-propenyl phosphate. All six metabolites were found in 24-h urine and 3-h bile, with bis(2-bromo-2-propenyl) phosphate and 2-bromo-2-propenyl phosphate predominating in urine, while bis(2,3-dibromopropyl) phosphate and 2-bromo-2-propenyl-2,3-dibromopropyl phosphate were the major metabolites identified in bile; 67% of urinary and 47% of biliary ^{14}C were accounted for by a variety of unidentified metabolites.

In vitro, liver microsomes from rat, mouse, hamster and guinea-pig all activate tris(2,3-dibromopropyl) phosphate resulting in covalent binding to protein. This binding was cytochrome P450-dependent and was inhibited by glutathione. *In vivo* in rats, the kidney was the principal target organ for covalent binding to protein and, at high doses, to DNA. This binding was enhanced by pretreatment with polychlorinated biphenyls but not sodium phenobarbital and was partly prevented by cobalt chloride ($CoCl_2$) pretreatment. There was much less binding to liver protein and DNA and minimal binding to muscle (Søderlund *et al*., 1981, 1982a).

Nelson *et al*. (1984) and Søderlund *et al.* (1984) identified the proximate mutagenic metabolite of tris(2,3-dibromopropyl) phosphate as 2-bromoacrolein and used stable

isotope techniques in microsomal incubations to show that it is formed by cytochrome P450-dependent oxidative debromination at C-3 of one of the 2,3-dibromopropyl groups followed by β-elimination to break the phosphoester bond. Søderlund *et al.* (1984) also showed the evolution of bromide ion release in microsomes in a glutathione-dependent reaction.

These studies have been extended by Pearson *et al.* (1993a,b), who showed that a number of metabolites contribute to protein binding in addition to 2-bromoacrolein. The major metabolic pathway leading to protein binding is C-2 oxidation of the 2,3-dibromopropyl groups, giving a reactive α-bromoketone which might either alkylate proteins directly or be hydrolysed to bis(2,3,-dibromopropyl) phosphate and an α-bromo-α′-hydroxyketone which could mediate the alkylation of protein.

4.2 Toxic effects

4.2.1 *Humans*

In a cohort of 3579 white male chemical workers with potential exposures to brominated compounds including tris(2,3-dibromopropyl) phosphate, no significant overall or cause-specific mortality excess was detected (Wong *et al*., 1984).

4.2.2 *Experimental systems*

Tris(2,3-dibromopropyl) phosphate caused extensive acute renal tubule necrosis at doses of 175 mg/kg bw and higher in male rats. Treatment also resulted in hepatotoxicity, but this effect was less pronounced and occurred at higher doses (Søderlund *et al*., 1980). Administration of radioactively labelled tris(2,3-dibromopropyl) phosphate to rats as a single intraperitoneal dose of 250 mg/kg bw led to pronounced binding of radioactivity to kidney but not to liver protein 9 h later (Dybing *et al*., 1980). Morales and Matthews (1980) and Lynn *et al*. (1982) also showed that the kidney accumulated the highest rate of radioactivity after injection of [^{14}C]tris(2,3-dibromopropyl) phosphate, compared with other organs. Dybing and Søderlund (1980) treated rats intraperitoneally with 250 mg/kg bw unlabelled tris(2,3-dibromopropyl) phosphate and determined parameters of kidney and liver toxicity 24 h later. The treatment resulted in increased plasma urea and creatinine levels. Kluwe *et al*. (1981) reported that tris(2,3-dibromopropyl) phosphate treatment of rodents resulted in decreased non-protein sulfhydryl content in the liver, but not in the kidney as the major target organ.

In young male Fischer 344 rats treated with 100 mg/kg bw tris(2,3-dibromopropyl) phosphate by gavage, severe tubular nephrosis was observed, starting from the corticomedullar junction and spreading to the peripheral cortex (Reznik *et al*., 1981). A single intraperitoneal dose of 154 mg/kg bw tris(2,3-dibromopropyl) phosphate given to male Sprague-Dawley rats caused cortical damage, significant increases in serum creatinine level and a depression of *para*-aminohippurate uptake in cortical slices (Elliott *et al*., 1982).

Cunningham *et al*. (1993, 1994) fed male Fischer 344 rats a diet containing 0, 50 or 100 ppm (mg/kg) tris(2,3-dibromopropyl) phosphate for 14 days. In the kidney, the

treatment induced significant cell proliferation that was localized in the renal outer medulla region. The proliferation rates of the inner medulla, the cortex and the liver were not increased.

In mice, hamsters and guinea-pigs, no clear evidence of renal damage was found at doses of 500–1000 mg/kg bw tris(2,3-dibromopropyl) phosphate (Søderlund *et al*., 1982a), which were clearly nephrotoxic to rats. Analysis of protein binding of radiolabelled tris(2,3-dibromopropyl) phosphate showed that binding to kidney protein also was much higher in rats than in the other species investigated.

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

In a study by Seabaugh *et al*. (1981), pregnant Sprague-Dawley rats received 0, 5, 25 or 125 mg/kg bw tris(2,3-dibromopropyl) phosphate by gavage on days 6–15 of gestation. Weight gain during gestation was significantly decreased in the animals treated with 125 mg/kg bw per day, but no other compound-related toxic or teratogenic effect was observed.

4.4 Genetic and related effects

The genotoxicity of tris(2,3-dibromopropyl)phosphate has been reviewed (van Beerendonk *et al*., 1994a).

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 3 for references)

Tris(2,3-dibromopropyl) phosphate is mutagenic in *Salmonella typhimurium* in the presence of a metabolic activation system and in V79 Chinese hamster lung cells. With or without metabolic activation, it produces sister chromatid exchanges in the latter system and morphological transformation in C3H 10T½ and Syrian hamster embryo cells. It binds covalently to proteins and DNA, and causes DNA single strand breaks in mammalian cells *in vitro* and *in vivo*. It is mutagenic (in somatic and germ cells), clastogenic and recombinogenic in *Drosophila melanogaster* and induces bone-marrow micronuclei in mice and hamsters, liver micronuclei in rats and gene mutations in mouse kidney *in vivo*.

4.4.3 *Mechanistic aspects*

Mechanistic and metabolic studies have suggested that the genotoxicity of tris(2,3-dibromopropyl) phosphate may be mediated by its conversion to reactive metabolites, the most important of which may be 2-bromoacrolein (Nelson *et al*., 1984; Søderlund *et al*.,

Table 3. Genetic and related effects of tris(2,3-dibromopropyl) phosphate

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS repair activity, *Salmonella typhimurium* TA1535/pSK1002 *umu* test	NT	+	14	Shimada *et al.*, 1989
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	+	5	Søderlund *et al*. (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	56	Salamone & Katz (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	+	9	Lynn *et al*. (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	35	Søderlund *et al*. (1982b)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	35	Holme *et al*. (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	NT	+	35	Søderlund *et al*. (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	+	9	Lynn *et al*. (1982)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	+	9	Zeiger *et al*. (1982)
DMM, *Drosophila melanogaster*, somatic mutation (and recombination)	+		1.74 µg/mL feed	Vogel & Nivard (1993)
DMM, *Drosophila melanogaster*, somatic mutation (and recombination)	+		87 µg/mL feed	van Beerendonk *et al*. (1994b)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		13960 µg/mL feed	van Beerendonk *et al*. (1994b)
DMN, *Drosophila melanogaster*, aneuploidy	+		13960 µg/mL feed	van Beerendonk *et al*. (1994b)
DIA, DNA strand breaks, rat hepatoma cell line (Reuber) *in vitro*	–	NT	35	Gordon *et al*. (1985)
DIA, DNA strand breaks, male Wistar rat liver and testicular cells *in vitro*	+	NT	3.5	Søderlund *et al*. (1992)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	150	Sala *et al*. (1982)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	NT	+	14	Holme *et al*. (1983)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	NT	+	14	Søderlund *et al*. (1985)
SIC, Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	+	+	17.2	Sala *et al*. (1982)
TCM, Cell transformation, C3H 10T½ mouse cells	–[c]	–[c]	80	Sala *et al*. (1982)
TCM, Cell transformation, C3H 10T½ mouse cells	+	NT	2	Schechtman *et al*. (1987)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	+	25	Sala *et al*. (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	NT	7	Gordon *et al*. (1985)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay	+	NT	7	Søderlund *et al*. (1985)
DVA, DNA single-strand breaks, male Wistar rat (various organs) cells *in vivo*	+		244 ip × 1	Søderlund *et al*. (1992)
DVA, DNA strand breaks, male Wistar rat kidney *in vivo*	+		25 ip × 1	Pearson *et al*. (1993b)
GVA, Gene mutation, *lac*I Big Blue® mouse kidney cells *in vivo*	+		600 po × 4	de Boer *et al*. (1996)
MVM, Micronucleus test, B6C3F$_1$ mouse bone-marrow cells *in vivo*	+		1020 ip × 2	Salamone & Katz (1981)
MVR, Micronucleus test, Wistar rat hepatocytes *in vivo*	+		174.5 (ph) ip × 1	van Beerendonk *et al*. (1994a)
MVC, Micronucleus test, Chinese hamster bone marrow *in vivo*	+		400 ip × 1	Sala *et al*. (1982)
BID, Binding (covalent) to DNA, Wistar rat liver and kidney *in vitro*	NT	+	350	Søderlund *et al*. (1981)
BIP, Binding (covalent) to microsomal proteins, Wistar rat liver and kidney *in vitro*	NT	+	43.5	Søderlund *et al*. (1981)
BVD, Binding (covalent) to DNA, male Wistar rat kidney and liver *in vivo*	+		250 ip × 1	Søderlund *et al*. (1981)
BVP, Binding (covalent) to proteins, male Wistar rat kidney and liver *in vivo*	+		50 ip × 1	Søderlund *et al*. (1981)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BVP, Binding (covalent) to proteins, male Wistar rat kidney, liver and testes *in vivo*	+		250 ip × 1	Pearson *et al*. (1993b)
SPM, Sperm morphology, B6C3F$_1$ mice *in vivo*	+		817 ip × 5	Salamone & Katz (1981)

[a] +, positive; (+), weak positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; ip, intraperitoneal; ph, partial hepatectomy; po, oral

[c] Positive only when 12-*O*-tetradecanoylphorbol 13-acetate (0.1 µg/mL) was added to the media for three days following the first 24 h of treatment.

1984). 2-Bromoacrolein and 2,3-dibromopropanal are mutagenic in *Salmonella typhimurium* TA100, with or without metabolic activation, cause single-strand breaks in DNA of a rat hepatoma cell line and morphological transformation of Syrian hamster embryo cells (Gordon *et al*., 1985). Furthermore, 2-bromoacrolein forms adducts with DNA which block DNA replication *in vitro*. It also induces DNA–protein cross-links in *Drosophila melanogaster* (van Beerendonk, 1992, 1994c).

An equimolar dose of the metabolite bis(2,3-dibromopropyl) phosphate was markedly more nephrotoxic and led also to damage of the descending loop of Henle. Intraperitoneal injection of bis(2,3-dibromopropyl) phosphate to Sprague-Dawley rats resulted in necrosis of the renal cortex, which was less severe in female than in male rats (Elliott *et al*., 1983). Renal dysfunction, as indexed by serum creatinine level and in-vitro renal cortical uptake of *para*-aminohippurate and *N*-methylnicotinamide, was similar in males and females. Evidence for the role of bis(2,3-dibromopropyl) phosphate and mono(2,3-dibromopropyl) phosphate as nephrotoxic metabolites of tris(2,3-dibromopropyl) phosphate was provided by Lynn *et al*. (1982), Søderlund *et al*. (1982b) and Fukuoka *et al*. (1988). In isolated proximal tubule cells from rat kidney, 100 μM bis(2,3-dibromopropyl) phosphate inhibited the uptake of α-methylglucose, a parameter that the authors used to assess cytotoxicity (Boogard *et al*., 1989).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

During the 1970s, tris(2,3-dibromopropyl) phosphate was produced in low volumes, with occupational exposure likely to have occurred in its production and use in the textile industry. It does not appear to have been produced since then. The primary exposure to the general population appears to have been through wearing clothing treated with the chemical.

5.2 Human carcinogenicity data

A small cohort study of workers exposed to tris(2,3-dibromopropyl) phosphate was uninformative.

5.3 Animal carcinogenicity data

Tris(2,3-dibromopropyl) phosphate was tested for carcinogenicity in mice and rats by oral administration. In mice, it produced benign and malignant tumours of the forestomach and lung in animals of each sex, benign and malignant liver tumours in females and benign and malignant tumours of the kidney in males. In rats, it produced benign and malignant tumours of the kidney in males and benign kidney tumours in females. In a study of limited duration in male rats, benign tumours of the colon were reported. After skin application to female mice, it produced tumours of the skin, lung, forestomach and oral cavity.

A metabolite of tris(2,3-dibromopropyl) phosphate, bis(2,3-dibromopropyl) phosphate, was tested for carcinogenicity in rats by oral administration and another metabolite, 2,3-dibromo-1-propanol, was tested in mice and rats by skin application. They produced a variety of tumours, including skin, forestomach and hepatocellular tumours, in mice and rats and tumours of the oesophagus, intestine, nasal mucosa and Zymbal glands in rats.

5.4 Other relevant data

Tris(2,3-dibromopropyl) phosphate and its metabolites bis(2,3-dibromopropyl)-phosphate and mono(2,3-dibromopropyl) phosphate are nephrotoxic in rodents.

Tris(2,3-dibromopropyl) phosphate is mutagenic in bacteria and causes genetic damage in cultured mammalian cells, *Drosophila melanogaster* and mice, probably via metabolism to a number of intermediates of which 2-bromoacrolein may be particularly important.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of tris(2,3-dibromopropyl) phosphate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tris(2,3-dibromopropyl) phosphate.

Overall evaluation

Tris(2,3-dibromopropyl)phosphate *is probably carcinogenic to humans (Group 2A).*

In making the overall evaluation, the Working Group took into consideration that tris(2,3-dibromopropyl) phosphate is consistently active in a wide range of mammalian in-vivo and in-vitro test systems.

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