International Journal of Toxicology
http://ijt.sagepub.com/

Chronic Toxicity and Carcinogenic Potential of Tris-(1,3-Dichloro-2-propyl) Phosphate in Sprague-Dawley Rat

Ralph I. Freudenthal and Richard T. Henrich

International Journal of Toxicology 2000 19: 119
DOI: 10.1080/109158100224926

The online version of this article can be found at:
http://ijt.sagepub.com/content/19/2/119

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
American College of Toxicology

Chronic Toxicity and Carcinogenic Potential of *Tris*-(1,3-Dichloro-2-propyl) Phosphate in Sprague-Dawley Rat

Ralph I. Freudenthal[1] and Richard T. Henrich[2]

[1]*West Palm Beach, Florida, USA*
[2]*Akzo Nobel Chemicals Inc., Dobbs Ferry, New York, USA*

The Flammable Fabrics Act of 1953 and its amendments established a need for flame-resistant fabrics. *Tris*-(1,3-dichloro-2-propyl) phosphate (TDCPP) was briefly used in apparel fabrics to assist in the compliance with federal flammability standards, and continues to be used as a flame retardant in flexible polyurethane foams. A chronic toxicity and carcinogenicity bioassay was conducted in Sprague-Dawley rats to determine the toxicologic and carcinogenic potential of TDCPP after repeated exposure. Four groups of animals, each consisting of 60 male and 60 female rats, received via their diet a daily dose of either 0, 5, 20, or 80 mg TDCPP per kg body weight for up to 24 months. Diets were adjusted after each weekly (first 13 weeks) or biweekly (weeks 14 through 104) body weight and food consumption measurement to achieve and maintain the indicated doses. Ten animals per sex were taken from each group for interim sacrifice at the end of the 12th month. Body weights, food consumption, clinical signs, and hematological and clinical chemistry parameters were measured periodically, and ophthalmoscopic examinations were conducted on all animals. After complete postmortem examination of all animals, microscopic examination of all tissues was conducted for the control and high-dose animals. Liver, kidneys, testes, and adrenal glands were examined from all animals. Mortality was significantly higher and body weights were significantly lower in the high-dose group when compared to control animals. Certain hematology parameters, such as hemoglobin, hematocrit, and total erythrocyte values, were decreased in the high-dose animals. Ophthalmoscope examination revealed no treatment-related changes. Microscopic examination revealed a higher incidence of benign neoplasms and non-neoplastic alterations in several organs of the mid and high dose animals. The no-observed-adverse-effect level (NOAEL) for chronic toxicity and neoplastic activity was the dietary dose of 5 mg/kg/day.

Keywords Carcinogenicity, Chronic Toxicity, Epigenetic, Flame Retardant, TDCPP, TRIS

Received 18 October 1999; accepted 10 December 1999.

The present address of Richard T. Henrich is Great Lakes Chemical Corporation, West Lafayette, Indianna, USA.

Address correspondence to Dr. Ralph I. Freudenthal, 8737 Estate Drive, West Palm Beach, FL 33411, USA.

The Flammable Fabrics Act of 1953 and its subsequent amendments established a need for flameproof fabrics. To meet the new flammability standards, manufacturers began using halogenated and phosphate-based chemicals to confer flame-resistant properties. One of the most widely used flame retardants was *tris*-(2,3-dibromopropyl) phosphate, commonly referred to as TRIS. In 1975 TRIS was shown to have significant mutagenic activity in several in vitro tests (Prival et al. 1977; Blum et al. 1978; Brusick et al. 1980; Holme et al. 1983). When TRIS was subsequently shown to be carcinogenic in rats and mice (National Cancer Institute 1978; Van Duuren et al. 1978), the product was banned for most uses. To maintain federal fabric flammability standards, several chemicals were substituted for TRIS. One of these replacement flame retardants was *tris*-(1,3-dichloro-2-propyl) phosphate (TDCPP), marketed as Fyrol FR-2.

In contrast to TRIS, TDCPP was shown to lack mutagenic activity in several in vitro and in vivo mutagenicity tests (Brusick et al. 1980; Holme and Soderlund 1984). The negative results in three Ames tests, a mouse lymphoma gene mutation assay, a rat hepatocyte unscheduled DNA repair assay, and a mouse bone marrow cytogenetics assay suggest TDCPP is not genotoxic. Whereas TRIS has teratogenic activity and has been shown to be a reproductive system toxin, TDCPP does not demonstrate either adverse effect (Osterberg, Bierbower, and Hehir 1977; Cochran and Wiedow 1986). Although the lack of mutagenic activity in nine mutagenicity tests provides a strong indication that TDCPP is not a genotoxic carcinogen, the manufacturer conducted a chronic toxicity and carcinogenicity bioassay, the results reported herein, to confirm the lack of carcinogenic activity.

MATERIALS AND METHODS

Test Substance

The test substance was identified as *tris*-(1,3-dichloro-2-propyl) phosphate (TDCPP) (CAS No. 13674-87-8), Lot Number 4670-23-3, manufactured by Stauffer Chemical Company

International Journal of Toxicology, 19:119–125, 2000

1091-5818/00 $12.00 + .00

Westport, Connecticut. It was a clear, somewhat viscous fluid. The purity of the test substance was 95%. TDCPP, a chemical shown to be highly stable even at elevated temperatures (boiling point 200°C), was stored at ambient temperature during the conduct of this study.

Test Animals

Male and female Sprague-Dawley CD rats (Charles River Laboratories, Wilmington, MA), about 5 weeks old, were acclimated for 3 weeks prior to being placed on study. The animals were individually housed in stainless steel cages with wire mesh floors and automatic water systems, and were maintained at a temperature of 21 ± 2°C and humidity of 55 ± 15%. The light cycle was controlled automatically to provide sequential light and dark periods of 12 hours each. Animals had ad libitum access to Purina Lab Chow and water throughout the study. Individual animals were assigned unique numbers and were identified by metal ear tag. All animals were observed twice daily for mortality and gross signs of toxicity, and were physically examined weekly. Body weights and food consumption were measured weekly for the first 13 weeks and biweekly between weeks 14 and 104.

Test Substance Administration

The doses used in this chronic bioassay were selected based on the results of an 8-week range-finding study. The test substance, TDCPP, was administered by blending into the animal diet to achieve doses of 0, 5, 20, or 80 mg/kg/day. Diets were blended weekly to maintain the target doses. Analyses were performed to assure that the mixing procedure produced homogeneous mixtures which were stable under use conditions.

Test Design

The study consisted of three exposure groups and a control group. Each of the four groups consisted of 60 male and 60 female animals. Ten male and 10 female rats were randomly selected from each group and sacrificed at the end of the 12th month. All surviving animals were sacrificed at the end of the 24th month. Ophthalmoscopic examinations were performed on all animals pretest and at 6-month intervals. Hematology, clinical chemistry, and urinary parameters were measured for 10 male and 10 female animals per group, at 3, 6, 12, 18, and 24 months. Blood was obtained by venipuncture from the orbital sinus under light anesthesia at interim collections and from the abdominal aorta at necropsy. The same animals were used at each collection interval where feasible. Freshly voided urine samples were examined for specific gravity, pH, protein, occult blood, and other endpoints. A summary of the study design is provided in Table 1.

Hematological parameters measured pretest and at the intervals specified above include hemoglobin, hematocrit, erythrocyte count, reticulocyte count, prothrombin time, partial thromboplastin time, and total and differential leukocyte counts. Clinical chemistry parameters determined at the same time points include serum glutamic pyruvic transaminase, alkaline phosphatase, blood urea nitrogen, fasting glucose, total protein, albumin, globulin, and the A/G ratio. Erythrocyte and plasma cholinesterase were determined at 18 and 24 months.

After 24 months, all surviving animals were euthanized by exanguination under anesthesia. Postmortem examinations were performed at necropsy and all major organs and tissues were preserved in 10% neutral-buffered formalin. Eyes, testes, and epididymides were initially fixed in Bouin's Solution for 48 to 72 hours before being placed in the buffered formalin. The following organs from all dose groups were weighed at necropsy: heart, thyroid, spleen, kidneys, liver, brain, pituitary, adrenals, and testes or ovaries.

The following tissues from the high-dose and control animals, and from all animals found dead or euthanized because of moribund condition, were examined microscopically: adrenal glands, abdominal aorta, bone and bone marrow, brain, epididymides, esophagus, eyes (with optic nerve), heart, intestine (cecum, colon, duodenum, ileum, jejunum), kidneys, liver, lungs (with main bronchi), lymph nodes, mammary gland, nerve

TABLE 1
Study design

Group number	Dose level (mg/kg/day)	Animals per group		Hematology, clinical chemistry*		Necropsy				Histopathology			
						12 month		24 month		12 month		24 month	
		M	F	M	F	M	F	M	F	M	F	M	F
1	0	60	60	10	10	10	10	50	50	10	10	50	50
2	5	60	60	10	10	10	10	50	50	**	**	**	**
3	20	60	60	10	10	10	10	50	50	**	**	**	**
4	80	60	60	10	10	10	10	50	50	10	10	50	50

*Hematology, clinical chemistry, and urinalysis performed at 3, 6, 12, and 24 months.
**Liver, kidneys, testes, and adrenal glands examined from mid- and low-dose animals.

(sciatic), ovaries, pancreas, pituitary gland, prostate, salivary glands (mandibular), seminal vesicles, skeletal muscle, skin, spinal cord (cervical), spleen, stomach, testes, thymus, thyroid (with parathyroids), trachea, urinary bladder, uterus, and vagina. Liver, kidneys, and testes were examined from animals in the low- and mid-dose groups also. Tissues were processed, trimmed, embedded in paraffin, cut at 6 microns, mounted, and stained with hematoxylin and eosin for microscopic examination.

Statistical Methods

Hematology and clinical chemistry data were analyzed using the Student's *t* test and *F* test, modified using Cochran's approximation (Snedecor and Cochran 1967). Differences in body weights, organ weights, and food consumption were examined using the Dunnett's Test (Dunnett 1964). Analysis of the tumor incidence data was by the Fisher Exact Test (one-tailed) (Bradley 1968). A p level of less than .05 ($p > .05$) was used as the critical level of significance for each statistical test.

RESULTS

Survival, Body Weights, and Food Consumption

The mortality rates were low in all groups during the first 12 months of the study (as shown in Table 2). During the 2nd year, there was a slight increase in mortality through month 18, after which mortality increased in all groups. Only the high-dose male animals had a significantly higher mortality than the control males. Body weights of the high dose animals were significantly lower throughout most of the study (Figure 1). Body weights of high-dose females were significantly lower from control values at all intervals (Figure 2). The differences in high-dose male rats were statistically significant beginning in week 7 and remained so through the rest of the study. The magnitude of the difference increased with time such that, at the end of the study, body weights of the high dose animals were more than 20% lower than the body weights of the control animals. The body weights of the mid- and low-dose animals were comparable to the control body weights, with few exceptions, as shown in Figures 1 and 2. Food consumption in the treated groups was similar to the food intake of the control animals throughout the study.

Hematology and Clinical Chemistry

Hemoglobin, hematocrit, and total erythrocyte values of the high-dose male and female animals were significantly lower than values for the control animals, whereas values for the mid- and low-dose animals were comparable to the control animals. All other hematological parameters were within the normal range. Serum alkaline phosphatase values for the high-dose animals were significantly lower than those of the control animals at most of the times measured. All other clinical chemistry endpoints were generally within normal range.

Organ Weights and Macroscopic Pathology

Liver weights of the high-dose animals (males and females) were significantly higher at both the 12- and 24-month necropsies. Although some animals in the mid-dose group also showed a significant increase in liver weight, the liver weights of the low-dose animals were comparable to the concurrent control animals. Kidney weights were significantly higher in the high-dose animals at both 12 and 24 months, and were higher in the mid-dose animals at the 24-month necropsy. Terminal organ weights and terminal organ to body weight ratios for the male and female animals are presented in Tables 3 and 4, respectfully. Gross postmortem examinations revealed a variety of abnormalities in the livers, kidneys, and testes of the treated animals, including discoloration, masses, nodules, and cysts. The mid- and high-dose male animals exhibited a higher incidence of small seminal vesicles and testicular enlargement, as compared to control males. However, the corresponding testes weights were not significantly higher than control weights.

Microscopic Observations

Microscopic examination of the many tissues listed herein revealed neoplastic and nonneoplastic alterations, primarily in the liver, kidneys, testes, and adrenal gland that occurred more

TABLE 2
Mortality incidence (% mortality)

Dose level (mg/kg/day)	Animals per group		Number of animals that died per group (% mortality)					
			12 Months		18 Months		24 Months	
	M	F	M	F	M	F	M	F
0	60	60	5 (8.3)	1 (1.7)	8 (13.3)	4 (6.7)	26 (43.3)	21 (35.0)
5	60	60	1 (1.7)	1 (1.7)	6 (10.0)	4 (6.7)	32 (53.3)	17 (28.3)
20	60	60	1 (1.7)	1 (1.7)	4 (6.7)	9 (15.0)	28 (46.7)	25 (41.7)
80	60	60	4 (6.7)	0 (0.0)	14 (23.3)	3 (5.0)	37 (61.7)*	25 (41.7)

*Statistically significant at $p < .05$.

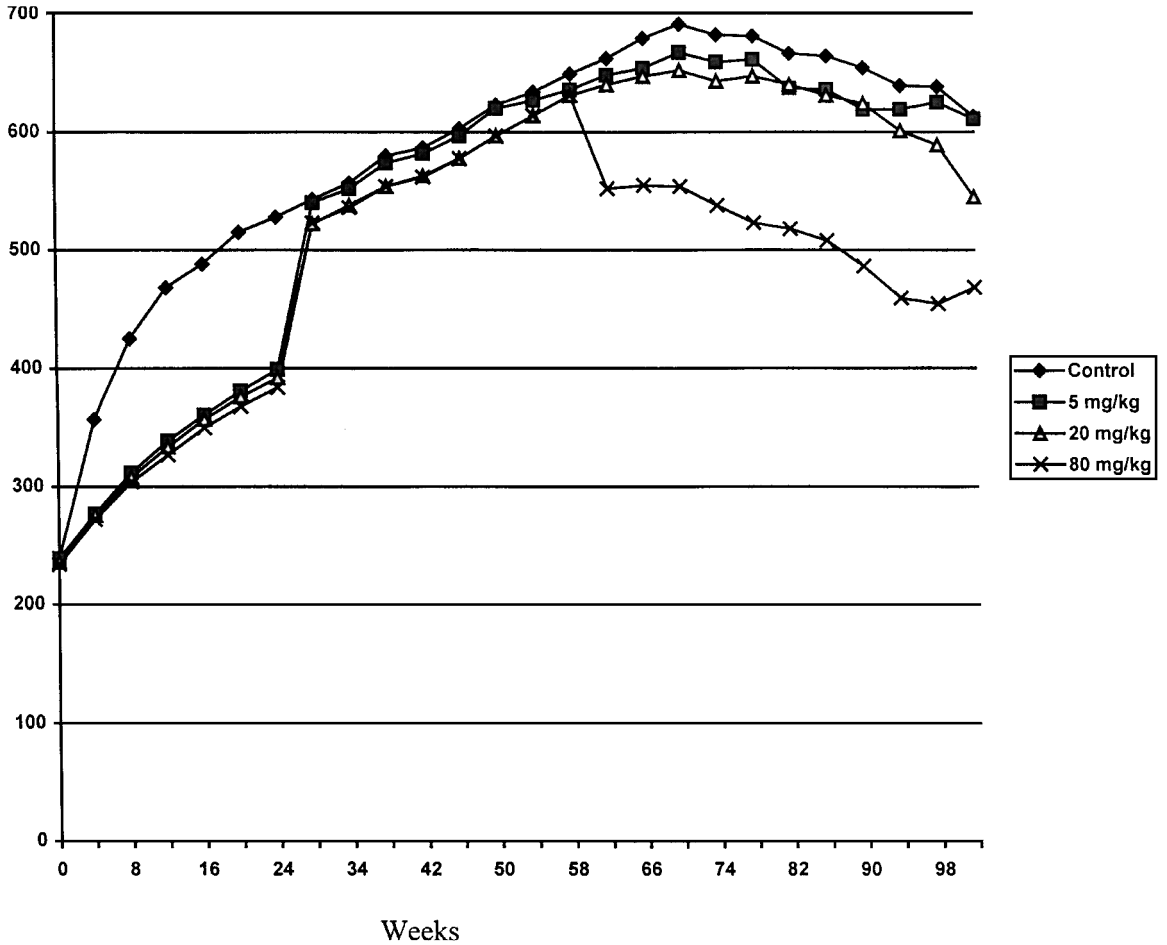

FIGURE 1

Male rat body weights (g). Effect of *tris*-(1,3-dichloro-2-propyl) phosphate on male Sprague-Dawley rat body weight gain during a 2-year dietary exposure.

frequently in TDCPP-treated animals than in control animals. Examination of the tissues from the 12-month interim group found an increased incidence of neoplastic nodules only in the kidneys of rats in the high-dose group, which were identified as renal cortical adenomas. The incidence of neoplasms in all other tissues were similar in control and treated animals.

An evaluation of the tissues from all study animals at the conclusion of the 24-month exposure period revealed a significant

TABLE 3

Terminal organ and body weights and organ/body weight ratios in male rats

Dose level	Terminal body weight	Brain		Testes		Kidneys		Liver		Thyroid	
		Weight	Ratio	Weight	Ratio	Weight	Ratio	Weight	Ratio	Weight	Ratio
0	612.13	2.17	0.362	3.14	0.509	3.74	0.626	14.43	2.400	0.040	0.0066
5	584.11	2.25	0.402	3.17	0.546	3.94	0.668	14.74	2.579	0.038	0.0068
20	507.50*	2.16	0.434*	2.64	0.501	5.49*	1.137*	16.33*	3.272	0.039	0.0079*
80	427.92*	2.17	0.515*	3.14	0.668	5.75*	1.345*	16.77*	3.999*	0.043	0.0102*

Note. Body and organ weights in grams; dose level is mg/kg/day.
*Statistically significant at $p < .05$.

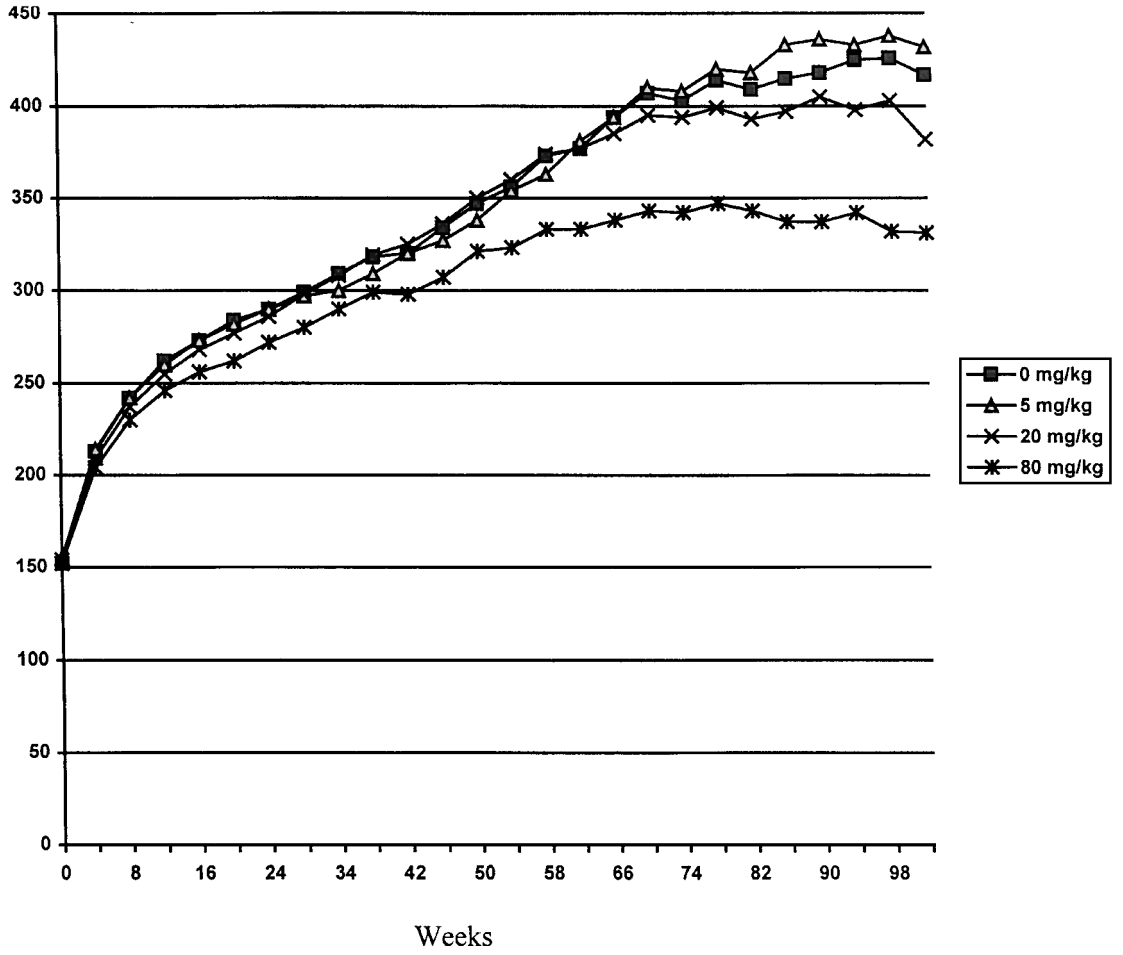

FIGURE 2

Female rat body weights (g). Effect of *tris*-(1,3-dichloro-2-propyl) phosphate on female Sprague-Dawley rat body weight gain during a 2-year dietary exposure.

increase in the incidence of renal cortical tumors and testicular interstitial cell tumors in the mid- and high-dose animals, and hepatocellular adenomas and adrenal cortical adenomas in the high-dose animals. The slight increase in hepatocellular carcinomas was not statistically significant when compared to concurrent controls. The tumor incidence for all dose groups at the end of 24 months is shown in Table 5. The no-observed-adverse-effect level (NOAEL) in this study is 5 mg/kg/day.

TABLE 4

Terminal organ and body weights and organ/body weight ratios in female rats

Dose level	Terminal body weight	Brain		Ovaries		Kidneys		Liver		Thyroid	
		Weight	Ratio	Weight	Ratio	Weight	Ratio	Weight	Ratio	Weight	Ratio
0	386.00	1.98	0.538	0.06	0.016	2.64	0.712	10.55	2.745	0.029	0.0077
5	403.56	1.95	0.502	0.06	0.015	2.96	0.739	11.27	2.804	0.030	0.0076
20	355.42	1.98	0.572	0.06	0.018	3.42*	0.983*	11.39	3.292*	0.030	0.0086
80	306.64*	1.96	0.659*	0.06	0.018	4.34*	1.401*	12.20	4.062*	0.034*	0.0114*

Note. Body and organ weights in grams; dose level is mg/kg/day.
*Statistically significant at $p > .05$.

TABLE 5
Tumor incidence after 24 months' ingestion of TDCPP

Organ	Tumor identification	Sex	Dose group (mg/kg/day) 0	5	20	80
Kidney	Renal cortical adenoma	M	1/45	3/49	9/48*	32/46*
		F	0/49	1/48	8/48*	29/50*
Testes	Interstitial cell tumor	M	7/43	8/48	23/47*	36/45*
Liver	Hepatocellular adenomas	M	2/60	7/56	1/58	16/59*
		F	1/60	1/60	4/55	9/58*
	Hepatocellular carcinomas	M	2/60	2/56	3/58	7/59
		F	1/60	2/60	2/55	4/58
Adrenal	Cortical adenomas	M	5/59	3/24	**	5/57
		F	8/48	5/27	2/33	19/49*

*Statistically significant at $p < .05$.
**Too few tissues available for accurate assessment.

DISCUSSION

The recognition that TRIS, a popular flame retardant used in a variety of products, was mutagenic and carcinogenic lead to the testing of replacement chemicals after the banning of TRIS by the Consumer Product Safety Commission. The structural similarity between TRIS and the popular replacement chemical, TDCPP, suggested an immediate need to evaluate the mutagenic potential of TDCPP. The product did not demonstrate mutagenic activity in the Ames test, mouse lymphoma gene mutation assay, hamster V79 cell test, rat primary hepatocyte DNA repair assay, mouse bone marrow cytogenetics assay, and a test with *Drosophila melanogaster* (Brusick et al. 1980; Holme and Soderlund 1984; Prival et al. 1977). In contrast, TRIS expressed significant mutagenic activity in each of these tests. A World Health Organization report describes extensive DNA damage found in several organs of rats administered TRIS (World Health Organization 1995). Although the consistent lack of mutagenic activity of TDCPP indicated the chemical does not have genotoxic activity and is not a genotoxic carcinogen, confirmation was necessary through additional testing.

Both TRIS and TDCPP were evaluated in an in vitro BALB/3T3 cell transformation assay used to predict carcinogenic potential. TRIS caused significant cell transformation whereas TDCPP was without activity (Brusick et al. 1980). The study reported herein was conducted to confirm the lack of carcinogenic activity in an in vivo bioassay. Rats received TDCPP in their diets, at either 0, 5, 20, or 80 mg/kg/day for up to 24 months. The body weight difference between the high-dose and control animals of more than 20% at the end of the study suggests the high dose most probably exceeded the maximum tolerated dose. The increased incidence of benign neoplasms in high-dose and mid-dose animals consisting of types of tumors normally found in aging Sprague-Dawley rats suggests TDCPP can exacerbate the development of spontaneously occurring tumors. Interstitial cell tumors of the testes can spontaneously occur in rats with an incidence as high as 90% (Derelanko and Hollinger 1995). In this study, 16% of the control animals had interstitial cell tumors. This commonly formed tumor does not metastasize and does not adversely affect an animal's life span. The hepatocellular adenomas, also described by the study pathologist as liver nodules, represent another benign tumor that is also found as a spontaneously occurring neoplasm in aging rats. Historically, the incidence of spontaneously occurring liver hyperplastic nodules/adenomas for Sprague-Dawley rats is reported to be 26.2 and 28.1% in male and female animals, respectively (Derelanko and Hollinger 1995). The incidence in this study was 27.1 and 15.5% in high dose male and female animals. This is well within the historical range. The historical incidence of hepatocellular carcinomas, 2.4% confirms that the few hepatocellular carcinomas observed in this study, in both control and treated animals, were also most probably spontaneously derived. A recently published comprehensive summary of tumor incidence per tissue in rat carcinogenicity bioassays reported 40% of the chemicals that demonstrated neoplastic activity induced liver tumors (Gold et al. 1991). In these bioassays, the liver consistently had the highest incidence of tumors of all tissues examined. It was therefore not unexpected that an increased incidence of liver tumors was reported in this study.

Adrenal cortical tumors also commonly occur in aging rats. In this study the control animals had an incidence of 17%. A significant increase in adrenal cortical adenomas was seen in the high-dose female rats. Benign renal cortical tumors are less common in Sprague-Dawley rats, spontaneously occurring at an incidence of about 2% (Derelanko and Hollinger 1995). In this study, the occurrence of this tumor increased significantly in the mid- and high-dose animals. Although the incidence of certain common spontaneously occurring tumors increased as a result of the chronic administration of TDCPP, they did not progress to malignancy.

Although the pathogenesis and mechanism by which these tumors arise have not been established, the consistent lack of mutagenic and genotoxic activity in both in vitro and in vivo mutagenicity assays suggests that the mechanism is via an epigenetic process. This is supported also by the lack of mutagenic metabolites of TDCPP.

TRIS has been shown to be a potent multiorgan genotoxic chemical that causes extensive DNA damage in various organs (Soderlund et al. 1992). Its mutagenic mechanism is via a reactive metabolite, 2-bromoacrolein, which is genotoxic and forms DNA adducts (Van Beerendonk et al. 1994). The metabolic activation of TRIS and the binding of a reactive metabolite to renal macromolecules has been demonstrated as a mechanism for the renal cancer induced by TRIS (Pearson et al. 1993). In contrast, the metabolites of TDCPP have been definitively identified, repeatedly tested for mutagenic potential, and have been consistently found to lack mutagenic activity (Nomeir, Kato, and Matthews 1981).

The available evidence supports the conclusion that daily chronic exposure of Sprague-Dawley rats to TDCPP resulted in the induction of benign tumors that are commonly found in aging rats. The epigenetic mechanism which exacerbated the spontaneously occurring tumor incidence did not induce the transformation of the benign tumors to a significant incidence of malignant neoplasms in any organ. Therefore, in this study, TDCPP increased the incidence of commonly occurring benign tumors but did not demonstrate carcinogenic activity.

REFERENCES

Blum, A., M. Gold, B. Ames, C. Kenyon, R. Dougherty, E. Horning, and J. Thenot. 1978. Children absorb tris-BP flame retardant from sleepwear: Urine contains the mutagenic metabolite 2,3-dibromopropanol. *Science* 201:1020–1024.

Bradley, J. 1968. *Distribution free statistical tests*. Englewood Cliffs, NJ: Prentice-Hall.

Brusick, D., D. Matheson, D. Jagannath, S. Goode, G. Roy, and S. Benson. 1980. A comparison of the genotoxic properties of tris(2,3-dibromopropyl) phosphate and tris(1,3-dichloro-2-propyl) phosphate in a battery of short-term bioassays. *J. Environ. Pathol. Toxicol.* 3:207–226.

Cochran, R., and M. Wiedow. 1986. The effects of tris(2,3-dibromopropyl) phosphate on the reproductive system of male rats. *J. Am. College Toxicol.* 5: 153–160.

Derelanko, M., and M. Hollinger. 1995. *CRC handbook of toxicology*. Boca Raton, FL: CRC Press.

Dunnett, C. 1964. New tables for multiple comparisons with a control. *Biometrics* 20:482–492.

Gold, L., T. Slone, N. Manley, and L. Bernstein. 1991. Target organs in chronic bioassays of 533 chemical carcinogens. *Environ. Health Perspect.* 93:233–284.

Holme, J., and J. Soderlund. 1984. Unscheduled DNA synthesis of the rat hepatocytes. *Mutat. Res.* 126:205–211.

Holme, J., J. Soderlund, S. Hongslo, and E. Dybing. 1983. Comparative genotoxicity studies of the flame retardant tris(2,3-dibromopropyl) phosphate and possible metabolites. *Mutat. Res.* 124:213–224.

National Cancer Institute, Carcinogenesis Testing Program. 1978. Bioassay of tris(2,3-dibromopropyl) phosphate for possible carcinogenicity. Carcinogenesis Technical Report Series Number 76.

Nomeir, A., S. Kato, and H. Matthews, 1981. The metabolism and disposition of tris(1,3-dichloro-2-propyl) phosphate (Fyrol FR-2) in the rat. *Toxicol. Appl. Pharmacol.* 57:401–413.

Osterberg, R., G. Bierbower, and R. Hehir. 1977. Renal and testicular damage following the dermal application of the flame retardant tris(2,3-dibromopropyl) phosphate. *J. Toxicol. Environ. Health* 3:979–987.

Pearson, P., J. Omichinski, R. McClanahan, and E. Soderlund. 1993. Metabolic activation of tris(2,3-dibromopropyl) phosphate to reactive intermediates. I. Covalent binding and reactive metabolite formation. *Toxicol. Appl. Pharmacol.* 118:186–195.

Prival, M., E. McCoy, B. Gutter, and H. Rosenkrantz. 1977. Tris(2,3-dibromopropyl) phosphate: Mutagenicity of a widely used flame retardant. *Science* 195:76–78.

Snedecor, G., and W. Cochran. 1967. *Statistical methods*, 6th ed. Ames, Iowa: Iowa State University Press.

Soderlund, E., G. Brunborg, E. Dybing, and B. Trygg. 1992. Organ-specific DNA damage of tris(2,3-dibromopropyl) phosphate and its diester metabolite in the rat. *Chem.-Biol. Interaction* 82:195–207.

Van Beerendonk, G., F. Van Gog, H. Vreiling, and P. Pearson. 1994. Blocking of an in vitro DNA replication and deoxycytidine adducts of the mutagen and clastogen 2-bromoacrolein. *Cancer Res.* 54:679–685.

Van Duuren, B., G. Loewengart, I. Seidman, and S. Melchionne. 1978. Mouse skin carcinogenicity tests of the flame retardants tris(2,3-dibromopropyl) phosphate, tetrakis(hydroxymethyl) phosphonium chloride, and polyvinyl bromide. *Cancer Res.* 38:3236–3240.

World Health Organization. 1995. Environmental Health Criteria Report on Tris(2,3-dichloropropyl) phosphate. 173:23–87.