

Evidence on the Carcinogenicity of Tris(1,3-Dichloro-2-Propyl) Phosphate

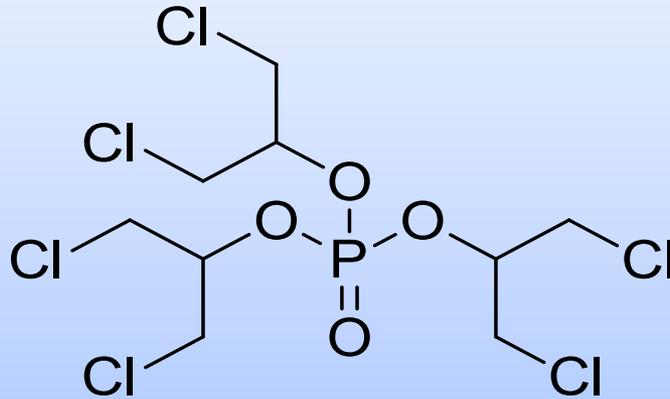
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October 12, 2011

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TDCPP Uses



CAS-RN: 13674-87-8

- High production volume chemical
- Additive flame retardant in flexible polyurethane foams:
 - Upholstered furniture and automotive products (e.g., sofas, car seats, seat cushions)



Occurrence

- Measured in indoor air and dust
- Detected in the environment
 - e.g., streams, sewage influent and effluent
- Detected in human tissues
 - Adipose tissue, seminal plasma, milk



Carcinogenicity Studies in Humans

- One unpublished retrospective cohort study of 289 workers at TDCPP plant (1956-1980)*
- 10 cancer deaths, SMR higher than expected
- Unable to draw conclusions (sample size, confounding)

*Stauffer Chemical Company, 1983b, as described by the European Commission, 2009, and ATSDR, 2009.



Carcinogenicity Studies in Animals

Studies in Rats

- Bio/dynamics, 1981; Freudenthal and Henrich, 2000
- Sprague-Dawley rats
 - 0, 5, 20, 80 mg TDCPP/kg-day in feed for two years
 - 60 animals/sex/dose
 - 24-month studies with 12-month interim sacrifice (10 animals/sex/dose)



Feed Studies in Rats

Liver Tumor Incidences

	Tumor type	Dose group (mg/kg/day)				Trend test (p-value)
		0	5	20	80	
Male rats	Hepatocellular adenoma	2/45	7/48	1/48	13/46**	<0.05
	Hepatocellular carcinoma	1/45	2/48	3/48	7/46*	<0.05
	Combined hepatocellular adenoma and carcinoma	3/45	9/48	4/48	20/46**	<0.05
Female rats	Hepatocellular adenomas	1/49	1/47	4/47	8/50*	<0.05
	Hepatocellular carcinoma	0/49	2/47	2/47	4/50	<0.05
	Combined hepatocellular adenoma and carcinoma	1/49	2/47	5/47	12/50**	<0.05

Significant by pairwise comparison with controls; * p<0.05, ** p<0.01



Feed Studies in Rats

Kidney Tumor Incidences

	Tumor type	Dose group (mg/kg/day)				Trend test (p-value)
		0	5	20	80	
Male rats	Renal cortical adenoma	1/45	3/49	9/48*	32/46**	<0.05
Female rats	Renal cortical adenoma	0/49	1/48	8/48**	29/50**	<0.05

Testes Tumor Incidences

	Tumor type	Dose group (mg/kg/day)				Trend test (p-value)
		0	5	20	80	
Male rats	Interstitial cell tumor	7/43	8/48	23/48*	36/46*	<0.05

Significant by pairwise comparison with controls; * p<0.05, ** p<0.01



Feed Studies in Rats

- Adrenal Gland Tumors in Females:
 - Significant increase in adrenal adenomas and combined adenomas and carcinomas.
 - Not significant by pairwise comparison when combined with interim sacrifice.



In Vitro Genotoxicity

- Positive
 - Multiple *Salmonella typhimurium* reverse mutation assays
 - TA 97, 98, 1537(+/-S9) frameshift mutations
 - TA 100 and TA 1535 (+/- S9) base-pair substitution mutations
 - Mutations in mouse lymphoma cells (+S9)
 - CA in mouse lymphoma (+/-S9) and Chinese hamster fibroblast cells (+S9)
 - SCE in mouse lymphoma cells (+/- S9)
- Negative
 - Some *Salmonella typhimurium* assays
 - One *Saccharomyces cerevesiae* reverse mutation (S4) (+/- S9)
 - Mutations in mouse lymphoma (+/- S9) and Chinese hamster fibroblast (+S9) cells
 - CA in CHO cells (+/-S9)



In Vivo Genotoxicity

- Positive
 - DNA binding in mouse liver, kidney & muscle
- Negative
 - SLRL mutations in *Drosophila*
 - CA in mouse bone marrow and chick embryo
 - Mouse bone marrow MN assay
 - Unscheduled DNA synthesis in rat hepatocytes

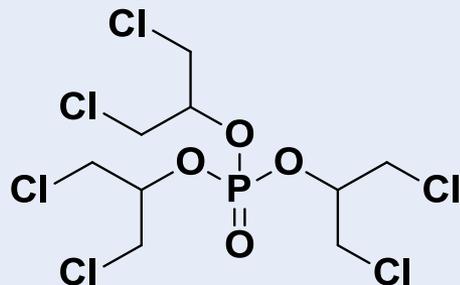


In Vitro Cell Transformation

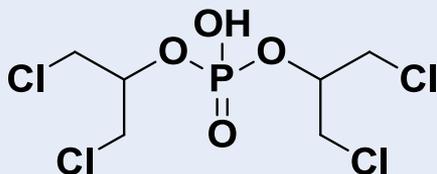
- Positive in Syrian hamster embryo cells (2 experiments)
- Negative in BALB/c 3T3 mouse cells



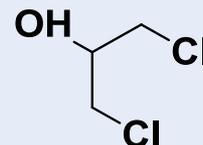
TDCPP and its Metabolites



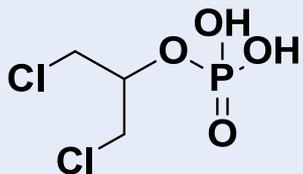
**tris(1,3-dichloro-2-propyl) phosphate
(TDCPP)**



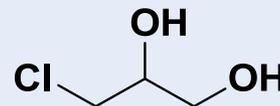
**bis(1,3-dichloro-2-propyl) phosphate
(BDCPP)**



**1,3-dichloro-2-propanol
(1,3-DCP)**



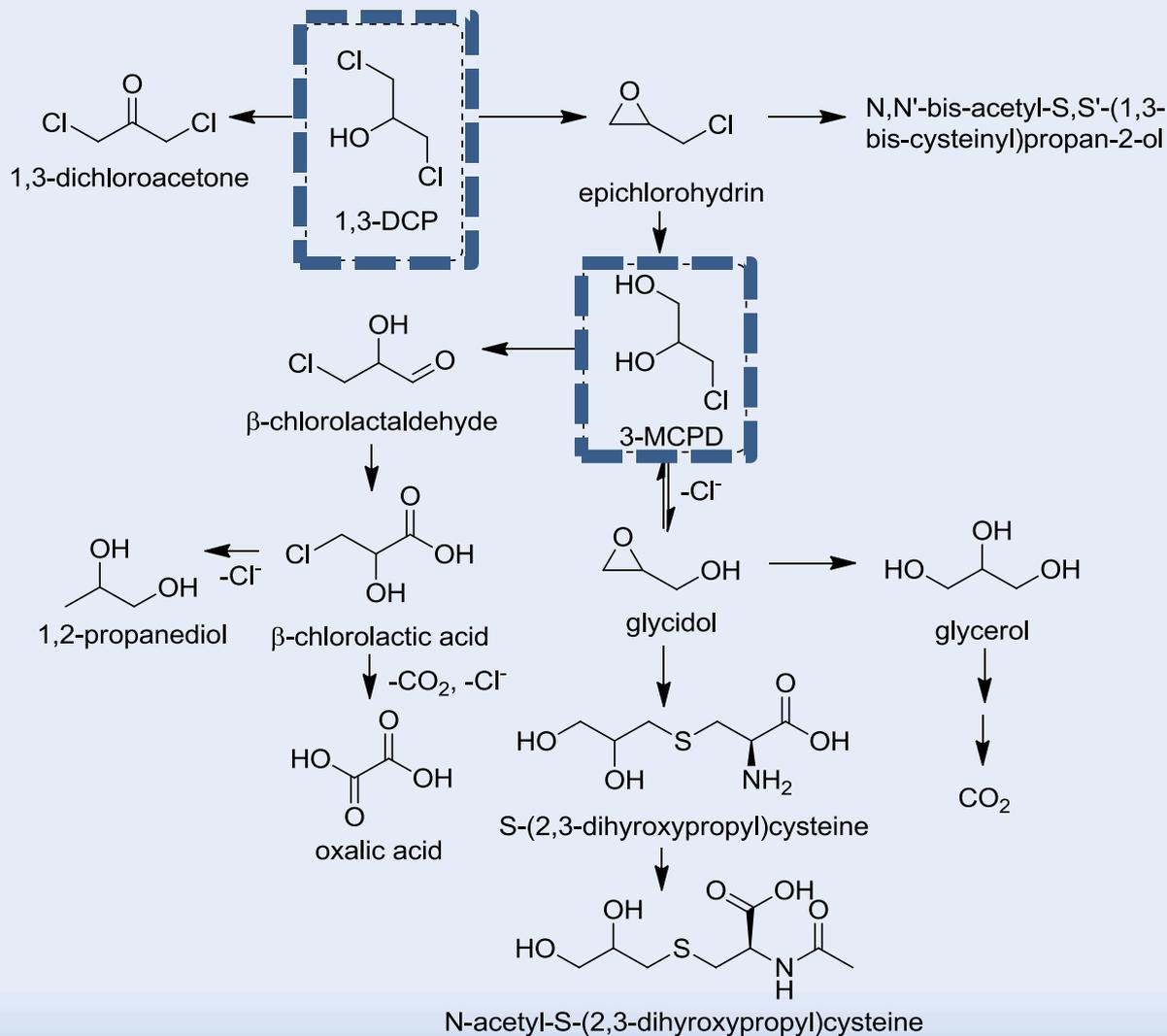
**1,3-dichloro-2-propyl phosphate
(MDCPP)**



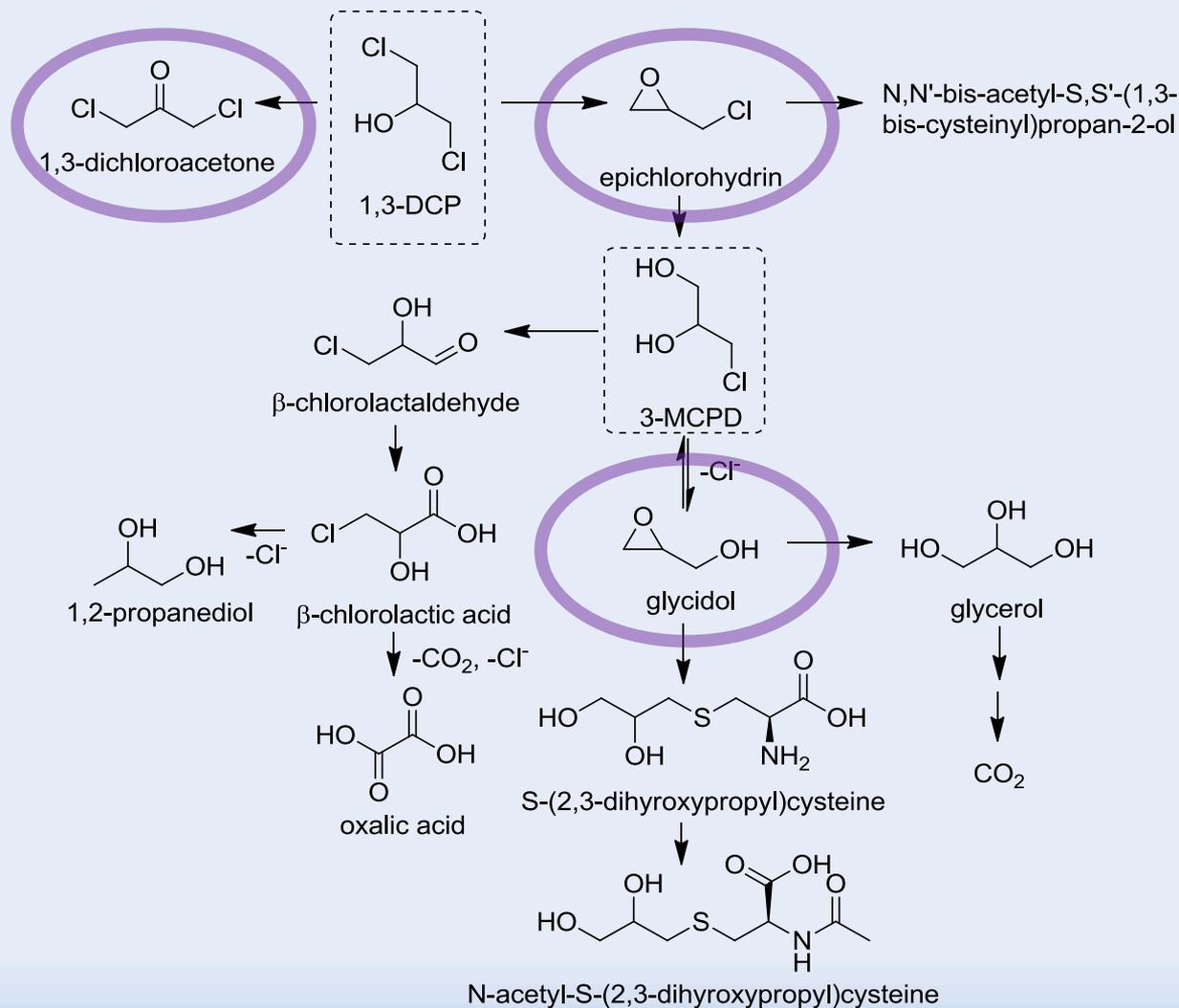
**3-monochloro-1,2-propanediol
(3-MCPD)**



Metabolism of 1,3-DCP and 3-MCPD



Metabolism of 1,3-DCP and 3-MCPD



Tumor Comparison for Metabolites

Chemical	Liver		Kidney		Testes		Thyroid		Other (e.g., tongue, mammary, lung, forestomach)	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
TDCPP		M F		M F		M				
1,3-DCP*		M F		M				M F		M F
3-MCPD*				M F		M				
Epichlorohydrin*										M F
Glycidol*	M						M	M	M F	M F

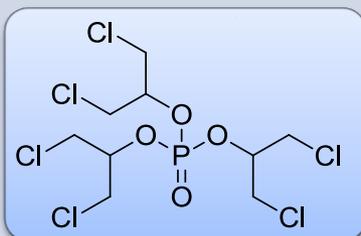
* Listed under Proposition 65



Structurally Related Chemicals

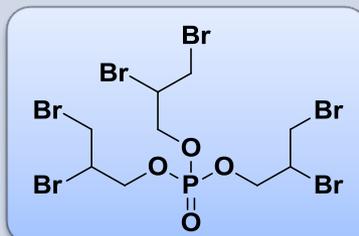
Chemical	Liver		Kidney		Testes		Thyroid		Other (e.g. lung, forestomach)	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
TDCPP		M F		M F		M				
TDBPP	F		M	M F						M F
TCEP			M	M F				M F	F	

Tris(1,3-Dichloro-2-Propyl) Phosphate (TDCPP)



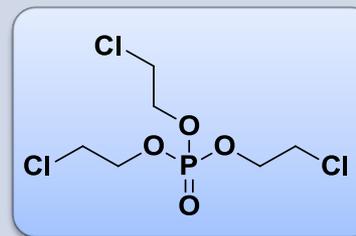
Under consideration

Tris(2,3-dibromopropyl) phosphate (TDBPP)



Prop 65 listed

Tris(2-chloroethyl) phosphate (TCEP)



Prop 65 listed



Possible Mechanisms of Action

- Genotoxicity
- Other



Summary of Evidence

Animal Evidence for Carcinogenicity

Male S-D rats

- Malignant and combined malignant and benign liver tumors
- Benign kidney tumors
- Testicular interstitial cell tumors

Female S-D rats

- Combined malignant and benign liver tumors
- Benign kidney tumors



Summary of Evidence (continued)

Other Relevant Data

- *In vitro* genotoxicity in a variety of systems
- Malignant transformation of cells
- Metabolism to the carcinogens 1,3-DCP and 3-MCPD
- Structurally similar to other halogenated phosphotriester carcinogens (TDBPP, TCEP)

