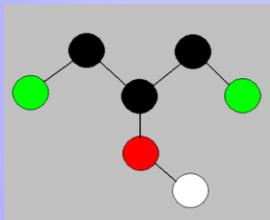


# HAZARD IDENTIFICATION EVIDENCE FOR 1,3-DICHLORO-2-PROPANOL (1,3-DCP)

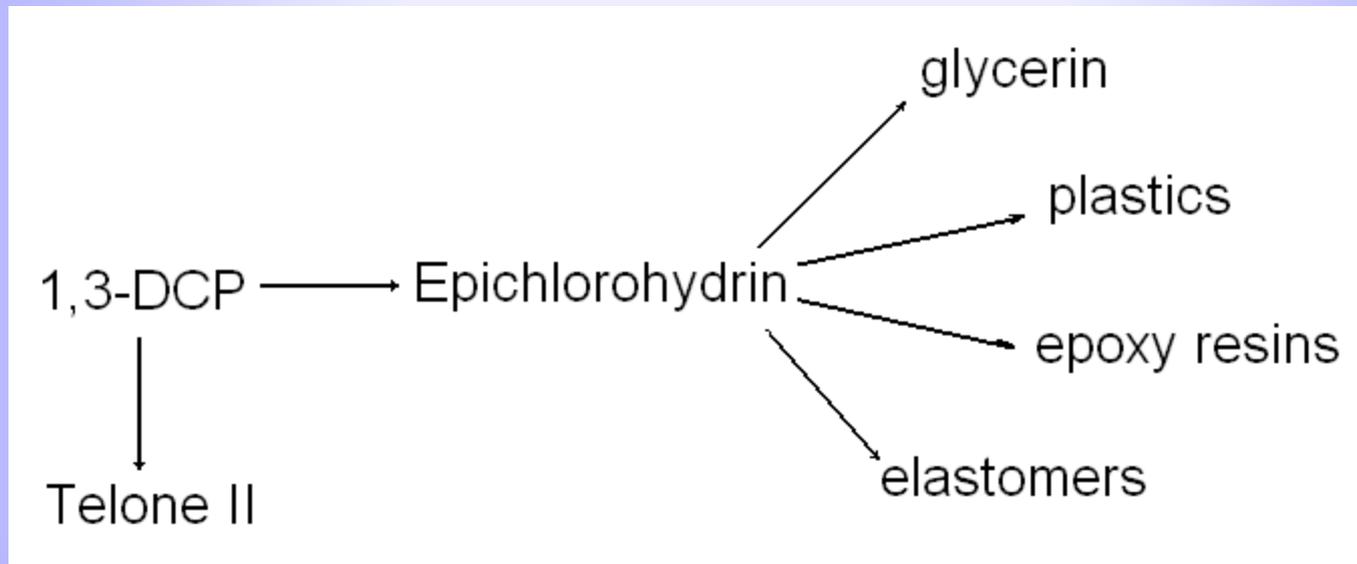
Cancer Toxicology and Epidemiology  
Section

Reproductive and Cancer Hazard  
Assessment Branch



# USE OF 1,3-DCP

1,3-DCP is a high production volume industrial chemical.



# 1,3-DCP in FOODS

- **Formed in some foods during processing**
- **Present in foods to which acid-hydrolyzed vegetable protein has been added**
- **From packaging**
- **Water treatment contaminant**



# OVERVIEW OF CARCINOGENICITY EVIDENCE

- **Animal Carcinogenicity Data (Hercules, 1989)**
- **Genotoxicity**
- ***In Vitro* Cell Transformation Assay**
- **Metabolism**
- **Structure Activity Considerations**
- **Possible Mechanisms**



# ANIMAL STUDIES

- **Carcinogenicity assays in male and female Wistar Han KFM rats, 104-weeks, drinking water**
- **Chronic toxicity assays in male and female Wistar Han KFM rats 26-, 52- and 78-weeks, drinking water**



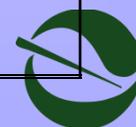
# 104-WEEK CARCINOGENICITY DRINKING WATER ASSAYS

- **Wistar Han KFM rats (50 each sex, dose)**
  - Male rats: 0, 2.1, 6.3, 19 mg/kg/day
  - Female rats: 0, 3.4, 9.6, 30 mg/kg/day
- **Complete histopathology**
  - All control & high-dose animals
  - Low- & mid-dose animals dying before week 104
- **Limited histopathology (adrenal, esophagus, kidney, lungs, thyroid, tongue)**
  - Low- & mid-dose animals surviving to week 104



# TUMOR INCIDENCES IN MALE RATS (1)

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	2.1	6.3	19
<b>KIDNEY</b>				
Tubular adenomas	0/50 p<.001	0/50	3/50	9/50 p<.05
Tubular carcinomas	0/50	0/50	0/50	1/50
Adenomas and carcinomas	0/50 p<.001	0/50	3/50	9/50 p<.05
<b>LIVER</b>				
Hepatocellular adenomas	1/50	0/50	0/50	0/50
Hepatocellular carcinomas	0/50 p<.001	0/50	2/50	8/50 p<.05
Adenomas and carcinomas	1/50 p<.001	0/50	2/50	8/50 p<.05
Hemangiosarcoma	0/50	0/50	0/50	1/50



# TUMOR INCIDENCES IN MALE RATS (2)

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	2.1	6.3	19
<b>THYROID</b>				
Follicular adenomas	0/50 p<.05	0/50	2/50	3/48
Follicular carcinomas	0/50	0/50	2/50	1/48
Adenomas and carcinomas	0/50 p<.05	0/50	4/50	4/48 p=.052
<b>TONGUE</b>				
Squamous cell papillomas	0/50 p<.001	1/50	0/49	6/50 p<.05
Squamous cell carcinomas	0/50 p<.001	0/50	0/49	6/50 p<.05
Papillomas and carcinomas	0/50 p<.001	1/50	0/49	12/50 p<.001
<b>OTHER ORAL CAVITY (NON-TONGUE)</b>				
Papillary carcinomas	0/50	0/50	0/50	2/50



# TUMOR INCIDENCES IN FEMALE RATS (1)

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	3.4	9.6	30
<b>LIVER</b>				
Hepatocellular adenomas	1/50 p<.05	1/50	1/50	5/50
Hepatocellular carcinomas	0/50 p<.001	0/50	1/50	36/50 p<.001
Adenomas & carcinomas	1/50 p<.001	1/50	2/50	41/50* p<.001
Hemangio-sarcoma	0/50	0/50	0/50	1/50

\*25% metastasized to lungs



## TUMOR INCIDENCES IN FEMALE RATS (2)

Tumor site/type	Dose (mg/kg bw/day)			
	0	3.4	9.6	30
<b>THYROID (follicular cells)</b>				
Adenomas	1/50	0/50	3/50	3/49
Carcinomas	0/50	0/50	0/50	2/49
Adenomas & carcinomas	1/50 P<.05	0/50	3/50	5/49
<b>TONGUE (squamous cells)</b>				
Papillomas	0/50 P<.001	0/50	0/50	7/49 P<.01
Carcinomas	0/50 P<.001	1/50	1/50	4/49 P=.056
Papillomas & carcinomas	0/50 P<.001	1/50	1/50	11/49 P<.001
<b>OTHER ORAL CAVITY (non-tongue)</b>				
Papillary carcinomas	0/50	0/50	1/50	0/50



# 78-WEEK CHRONIC TOXICITY STUDY – MALE RATS

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	2.1	6.3	19
<b>KIDNEY</b>				
Renal tubular adenoma	0/10	0/10	0/10	1/10
<b>LIVER</b>				
Hepatocellular carcinoma	0/10 p<.05	0/10	0/10	3/10
<b>THYROID</b>				
Thyroid follicular adenoma	0/10	0/10	1/10	0/10
<b>TONGUE</b>				
Squamous cell carcinoma	0/10	0/10	1/10	0/10



# 78-WEEK CHRONIC TOXICITY STUDY – FEMALE RATS

Tumor Site/Type	Dose (mg/kg bw/day)			
	0	3.4	9.6	30
<b>LIVER</b>				
Hepatocellular carcinoma	0/10 p<.001	0/10	0/10	7/10 p<.01
<b>TONGUE</b>				
Squamous cell papilloma	0/10	0/10	0/10	1/10



# ***IN VITRO* GENOTOXICITY DATA**

- **Positive in numerous *in vitro* assays in**
  - *Salmonella* reverse mutation assays
    - TA 97 and 98 (+S9) frameshift mutations
    - TA 100 and 1535 (+/- S9) base pair mutations
  - *Salmonella* forward mutation assays (+/- S9)
  - *E. coli* reverse mutation (+ S9)
  - *E. coli* DNA repair (+ S9)
  - Mammalian cell (mouse and human) mutation (+/- S9)
  - SCE in hamster (V79 and CHO) cells (+/- S9)
  - Chromosome aberrations in CHO cells (+/- S9)



# ***IN VIVO* GENOTOXICITY DATA**

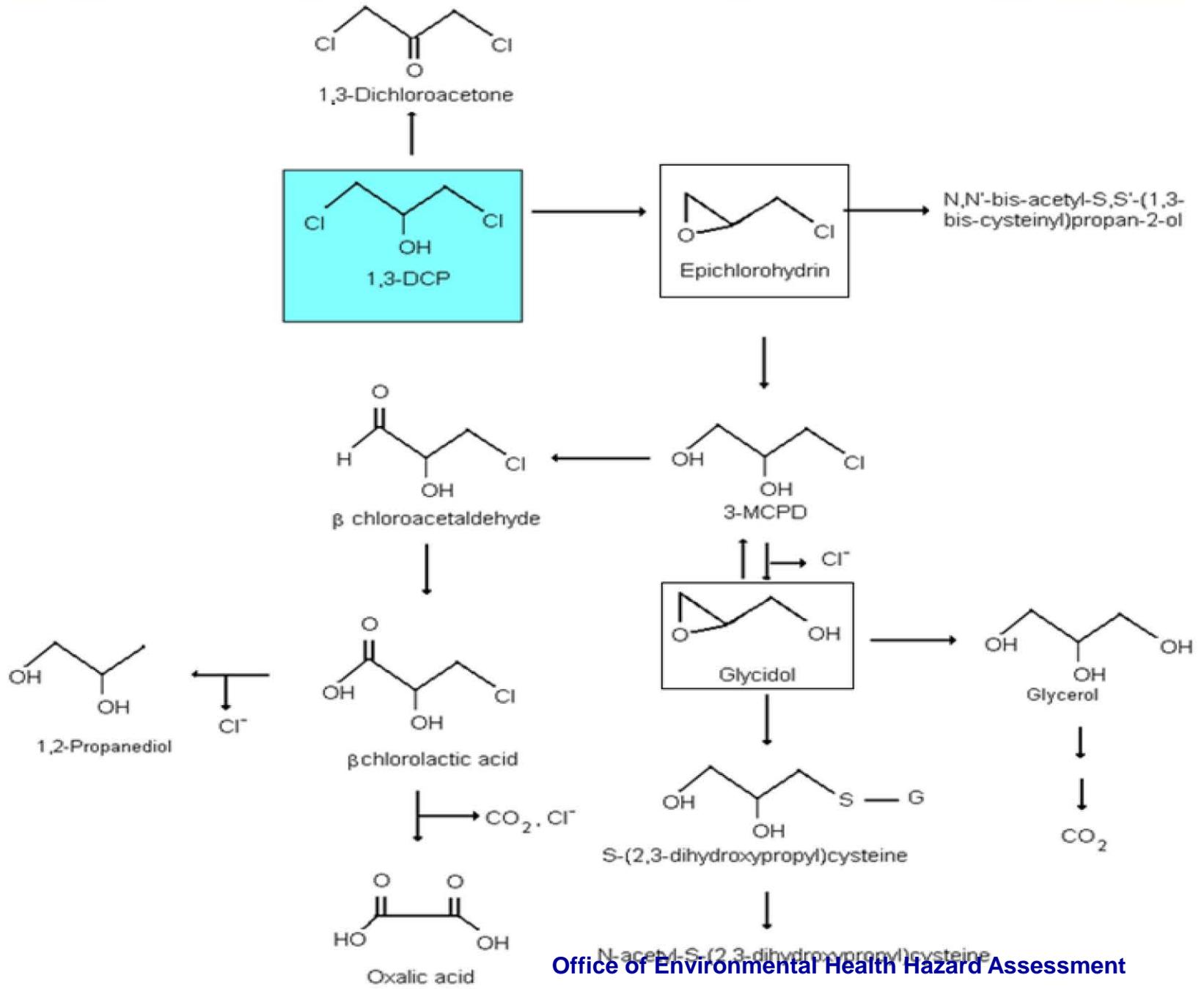
- **Negative in three *in vivo* assays in**
  - *Drosophila* somatic mutation (wing spot)
  - Wistar rat bone marrow micronucleus
  - Wistar rat unscheduled DNA synthesis (UDS)



# MOUSE CELL *IN VITRO* MALIGNANT TRANSFORMATION ASSAY

Number of transformed foci/number of treated dishes	1,3-DCP concentration ( $\mu\text{g/mL}$ )			
	Control	100	250	500
	0/24	7/14 $p < .001$	15/15 $p < .001$	3/14 $p < .05$



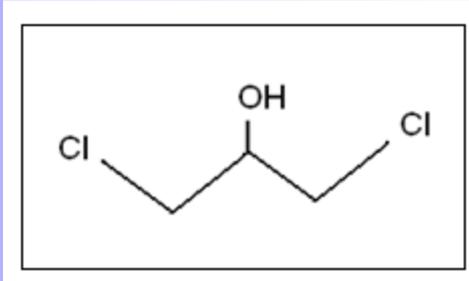


# STRUCTURE ACTIVITY CONSIDERATIONS

- **1,3-DCP and ten other structurally related halogenated compounds**
- **Seven of these are IARC and Proposition 65 carcinogens**

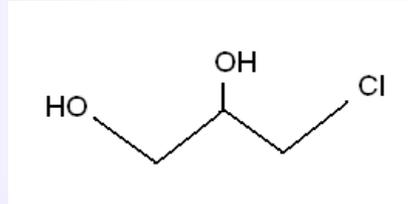


# Halogenated Propanols



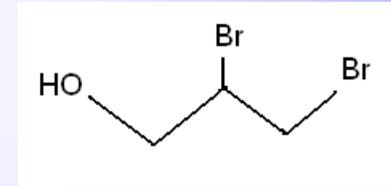
**1,3-DCP**

- Not evaluated by IARC



**3-MCPD**

- Not evaluated by IARC



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

- IARC 2B
- Proposition 65

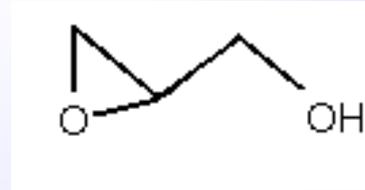


# Three-carbon epoxides



**Epichlorohydrin**

- IARC 2A
- Proposition 65

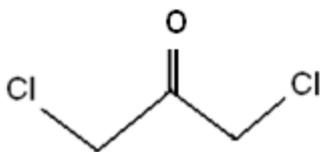


**Glycidol**

- IARC 2A
- Proposition 65

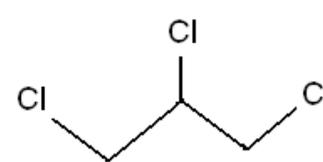


# Other three-carbon halogenated compounds



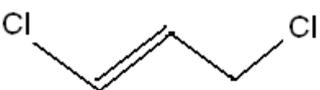
**1,3-  
Dichloroacetone**

- Not evaluated by IARC or Proposition 65



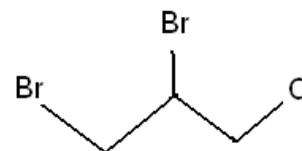
**1,2,3-  
Trichloropropane**

- IARC 2A
- Proposition 65



**Telone II**

- IARC 2B
- Proposition 65

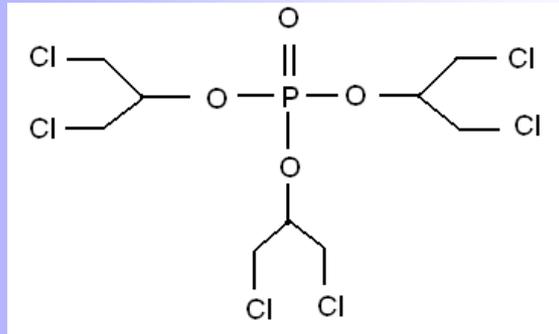


**DBCP**

- IARC 2B
- Proposition 65

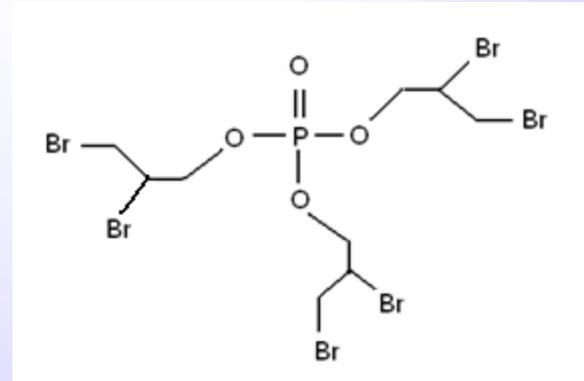


# Phosphate triesters



**TDCPP**

- Not evaluated by IARC or Proposition 65



**TDPP**

- IARC 2A
- Proposition 65



# TUMOR SITE CONCORDANCE

Chemical	Liver		Kidney		Thyroid		Tongue or oral cavity	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
1,3-DCP		M F		M		M F		M F
3-MCPD				M F				
Glycidol	M				M	M		F
2,3-Dibromo-1-propanol	M	M F						F
1,2,3-Trichloropropane	M F			M			F	M F
Telone II		M						
DBCP				M F				M F
TDCPP		M F		M F				
TDPP	F		M F	M F				M F



# POSSIBLE MECHANISMS

- **Genotoxicity**
- **Hepatotoxicity → hepatocarcinogenesis**
- **Direct contact carcinogenicity (tongue and oral cavity)**



# SUMMARY OF EVIDENCE

- **Animal evidence for carcinogenicity**
  - Tumors in both sexes of the rat (only species tested)
  - Tumors at multiple sites in males and females, including rare tongue tumors
  - Dose response
- **Genotoxicity in multiple *in vitro* assays with or without S9**
- ***In vitro* malignant transformation assay**
- **Metabolism to two epoxide carcinogens**
- **Structure activity considerations**
  - Structurally similar to seven carcinogens

