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

John B. Faust, Ph.D.
Laura Meehan August, M.P.H.

October 12, 2011

Cancer Toxicology and Epidemiology Section
Reproductive and Cancer Hazard Assessment Branch
TDCPP Uses

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

CAS-RN: 13674-87-8
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• One unpublished retrospective cohort study of 289 workers at TDCPP plant (1956-1980)*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

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Dose group (mg/kg/day)</th>
<th>Trend test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td><strong>Male rats</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular adenoma</td>
<td>2/45</td>
<td>7/48</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1/45</td>
<td>2/48</td>
</tr>
<tr>
<td>Combined hepatocellular adenoma and carcinoma</td>
<td>3/45</td>
<td>9/48</td>
</tr>
<tr>
<td><strong>Female rats</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatocellular adenomas</td>
<td>1/49</td>
<td>1/47</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>0/49</td>
<td>2/47</td>
</tr>
<tr>
<td>Combined hepatocellular adenoma and carcinoma</td>
<td>1/49</td>
<td>2/47</td>
</tr>
</tbody>
</table>

Significant by pairwise comparison with controls; * p<0.05, ** p<0.01
# Feed Studies in Rats

## Kidney Tumor Incidences

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Dose group (mg/kg/day)</th>
<th>Trend test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male rats Renal cortical adenoma</td>
<td>1/45 3/49 9/48* 32/46**</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Female rats Renal cortical adenoma</td>
<td>0/49 1/48 8/48** 29/50**</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

## Testes Tumor Incidences

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Dose group (mg/kg/day)</th>
<th>Trend test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male rats Interstitial cell tumor</td>
<td>7/43 8/48 23/48* 36/46*</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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 cerevisiae* 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

1,3-dichloroacetone \rightarrow \text{epichlorohydrin} \rightarrow N,N'-\text{bis-acetyl-S,S'}-(1,3-bis-cysteinyl)propan-2-ol

\beta\text{-chlorolactaldehyde} \rightarrow \beta\text{-chlorolactic acid} \rightarrow 1,2\text{-propanediol}

3-MCPD \rightarrow \text{glycidol} \rightarrow \text{glycerol}

\text{N-acetyl-S-(2,3-dihydroxypropyl)cysteine}

\text{oxalic acid}
Metabolism of 1,3-DCP and 3-MCPD

1,3-dichloroacetone → 1,3-DCP → epichlorohydrin → N,N'-bis-acetyl-S,S'-(1,3-bis-cysteiny1)propan-2-ol

β-chlorolacta1dehyde → 1,2-propanediol → β-chlorolactic acid → oxalic acid

3-MCPD → glycidol → glycerol → CO₂

S-(2,3-dihydroxypropyl)cysteine

N-acetyl-S-(2,3-dihydroxypropyl)cysteine
## Tumor Comparison for Metabolites

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Liver</th>
<th>Kidney</th>
<th>Testes</th>
<th>Thyroid</th>
<th>Other (e.g., tongue, mammary, lung, forestomach)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mice</td>
<td>Rats</td>
<td>Mice</td>
<td>Rats</td>
<td>Mice</td>
</tr>
<tr>
<td>TDCPP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,3-DCP*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-MCPD*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epichlorohydrin*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycidol*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Listed under Proposition 65
# Structurally Related Chemicals

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Liver</th>
<th>Kidney</th>
<th>Testes</th>
<th>Thyroid</th>
<th>Other (e.g. lung, forestomach)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>TDCPP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDBPP</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>TCEP</td>
<td></td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
</tr>
</tbody>
</table>

- **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)