TDCPP:
Assessment of Evidence Using
CIC’s “Known to the State to Cause Cancer” Under Proposition 65

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on behalf of
Albemarle Corporation
and
ICL-IP America Inc.
Summary

Previous assessments of TDCPP by authorities
  • None have concluded that there is “clear” evidence

“if the weight of scientific evidence clearly shows that a certain chemical causes invasive cancer in humans, or that it causes invasive cancer in animals (unless the mechanism of action has been shown not to be relevant to humans)” [CIC, 2001]
Summary

Using the CIC’s Prioritization Scheme:

• Direct Evidence
  – No human data supporting listing
  – Single 1981 animal study does not support listing (*limited evidence*)

• Indirect Evidence
  – *In vivo* genotoxicity data all negative
  – *In vitro* genotoxicity data does not support listing (less pertinent than *in vivo*)
  – TDCPP differs from other structurally-similar compounds
Evidence in Humans - None

• No evidence that TDCPP causes cancer in humans
  – Epidemiological data on TDCPP is limited
  – Data provide no evidence of causation of cancer of any type, including invasive cancer
  – Stauffer, 1983 involving manufacturing personnel
Single Animal Carcinogenicity Study – No Relevant Invasive Tumors

• Single animal bioassay report - Bio/dynamics, 1981
• Pre-GLP
• Not to current EPA Guidelines
• Tumors were reported at several sites
  – Tumors either
    • Non-invasive
    • Misclassified by modern histological protocol
    • Observed only well above MTD
CIC Weight of Evidence Guidance

CIC specifies that a single study in one species might be considered sufficient:

• “if the malignant tumors occurred to an unusual degree with respect to frequency, type, location, age at onset, or low dosage, or in a strain not otherwise prone to such tumors.

• “if heavily supported by the indirect evidences”
TDCPP is not Genotoxic

• The weight of the evidence demonstrates that TDCPP is not genotoxic.
• All in vivo data are negative
• EU conclusion (ECHA, 2010)
  – “Regarding notably the five negative in vivo assays, it is considered that TDCP[P] is not genotoxic in vivo and thus no classification for mutagenicity is proposed [for the EU].”
• New studies produced for EU authorities are negative
  – Unscheduled DNA synthesis in hepatocytes (Cifone, 2005)
  – Chromosomal aberrations in CHO cells (Murli, 2004)
<table>
<thead>
<tr>
<th>Substance name</th>
<th>CASRN</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)</td>
<td>13674-87-8</td>
<td><img src="image1" alt="Structure of TDCPP" /></td>
</tr>
<tr>
<td>Tris(2,3-dibromopropyl) phosphate (TDBPP)</td>
<td>126-72-7</td>
<td><img src="image2" alt="Structure of TDBPP" /></td>
</tr>
<tr>
<td>Tris(2-chloroethyl) phosphate (TCEP)</td>
<td>115-96-8</td>
<td><img src="image3" alt="Structure of TCEP" /></td>
</tr>
<tr>
<td>Tris(1-chloro-2-propyl) phosphate (TCPP)</td>
<td>13674-84-5</td>
<td><img src="image4" alt="Structure of TCPP" /></td>
</tr>
<tr>
<td>2,2-bis(chloroethyl)trimethylene bis[bis(2-chloroethyl)phosphate (V6)]</td>
<td>38051-10-4</td>
<td><img src="image5" alt="Structure of V6" /></td>
</tr>
</tbody>
</table>
TDCPP

**Not Clearly Shown to be Carcinogenic**

- The weight of evidence conclusion is that TDCPP has not been clearly shown to be carcinogenic.
  - No evidence in humans
  - Single non-guideline animal bioassay not “clearly shown to be carcinogenic” using the criteria establish by the CIC (2001)
  - Non-genotoxic
  - Differs from other structurally similar compounds
Adrenal Gland Tumors – Non-invasive

- Cortical adenomas of the adrenal gland
  - Significant in the high dose group of female rats
  - MTD was significantly exceeded
  - Non-invasive - did not progress to malignancy
Adrenal Gland Tumor Incidence in Female Rats Treated with TDCPP
(Data from Bio/dynamics, 1981)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Tumor</th>
<th>0 mg/kg/day</th>
<th>5 mg/kg/day</th>
<th>20 mg/kg/day</th>
<th>80 mg/kg/day</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td>Cortical adenoma</td>
<td>8/48</td>
<td>5/27</td>
<td>2/33</td>
<td>19/49*</td>
<td>Noninvasive tumor with high spontaneous incidence that is only increased at excessive dose level</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>5/11</td>
<td>0/0</td>
<td>0/0</td>
<td>1/10</td>
<td></td>
</tr>
</tbody>
</table>

* Identified by the study authors as significantly different from control (P<0.05)
Testes Tumors –
Non-invasive and not relevant

- Interstitial (Leydig) cell tumors of the testes
  - Non-invasive - does not progress to malignancy
  - Not relevant to humans
## Testes Tumor Incidence in Male Rats Treated with TDCPP

(Data from Bio/dynamics, 1981)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Tumor</th>
<th>0 mg/kg/day</th>
<th>5 mg/kg/day</th>
<th>20 mg/kg/day</th>
<th>80 mg/kg/day</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testes</td>
<td>Interstitial (leydig) cell tumor 12 months</td>
<td>7/43</td>
<td>8/48</td>
<td>23/47*</td>
<td>36/45*</td>
<td>Noninvasive tumor that has limited relevance for humans</td>
</tr>
<tr>
<td></td>
<td>0/14</td>
<td>0/12</td>
<td>3/13</td>
<td>3/11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Identified by the study authors as significantly different from control (P<0.05)
Kidney Tumors – Non-invasive

• Renal cortical adenomas
  – Non-invasive
  – No progression observed in these lesions
## Kidney Tumor Incidences in Male and Female Rats Treated with TDCPP
(Data from Bio/dynamics, 1981)

<table>
<thead>
<tr>
<th>Organ, Sex</th>
<th>Tumor</th>
<th>0 mg/kg/day</th>
<th>5 mg/kg/day</th>
<th>20 mg/kg/day</th>
<th>80 mg/kg/day</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney, male</td>
<td>Renal cortical adenoma</td>
<td>1/45</td>
<td>3/49</td>
<td>9/48*</td>
<td>32/46*</td>
<td>Noninvasive tumor that may be associated with tubular epithelial cell hyperplasia</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>0/15</td>
<td>0/12</td>
<td>0/13</td>
<td>0/13</td>
<td></td>
</tr>
<tr>
<td>Kidney, female</td>
<td>Renal cortical adenoma</td>
<td>0/49</td>
<td>1/48</td>
<td>8/48*</td>
<td>29/50*</td>
<td>Noninvasive tumor that may be associated with tubular epithelial cell hyperplasia</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>0/11</td>
<td>0/13</td>
<td>0/9</td>
<td>0/10</td>
<td></td>
</tr>
</tbody>
</table>

* Identified by the study authors as significantly different from control (P<0.05)
Liver Tumors

• Liver tumors generally within historical range for Sprague-Dawley CD rats
• Hepatocellular adenomas
  • Non-invasive
  • Mid- and low-dose groups are in the expected range for Sprague-Dawley rats (McMartin et al., 1992 (1984-1991))
• High-dose male and female incidence rates were elevated
• High-dose results impacted by MTD
  – Hepatocellular carcinomas (males) only at clearly excessive dose
## Liver Tumor Incidence in Male Rats Treated with TDCPP
(Data from Bio/dynamics, 1981)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Tumor</th>
<th>0 mg/kg/day</th>
<th>5 mg/kg/day</th>
<th>20 mg/kg/day</th>
<th>80 mg/kg/day</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Hepatocellular adenoma</td>
<td>2/45</td>
<td>7/48</td>
<td>1/48</td>
<td>13/46</td>
<td>Noninvasive lesion originally described as a “nodule” would now be separated into hyperplasia and adenoma</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>0/15</td>
<td>0/12</td>
<td>0/13</td>
<td>3/14</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
<td>1/45</td>
<td>2/48</td>
<td>3/48</td>
<td>7/46#</td>
<td>Increased only at excessive dose level</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>0/15</td>
<td>0/12</td>
<td>0/13</td>
<td>0/14</td>
<td></td>
</tr>
</tbody>
</table>

# Identified by the original study authors as different from control (p=0.06). Not indicated in ECHA (2010) or Frudenthal & Henrich (2000)
# Liver Tumor Incidence in Female Rats Treated with TDCPP
(Data from Bio/dynamics, 1981)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Tumor</th>
<th>0 mg/kg/day</th>
<th>5 mg/kg/day</th>
<th>20 mg/kg/day</th>
<th>80 mg/kg/day</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Hepatocellular adenoma</td>
<td>1/49</td>
<td>1/47</td>
<td>4/46</td>
<td>8/50</td>
<td>Noninvasive lesion originally described as a “nodule” would now be separated into hyperplasia and adenoma.</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>0/11</td>
<td>0/13</td>
<td>0/9</td>
<td>1/10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma</td>
<td>0/49</td>
<td>2/47</td>
<td>2/46</td>
<td>4/50</td>
<td>Not significant increase only at excessive dose level</td>
</tr>
<tr>
<td></td>
<td>12 months</td>
<td>0/11</td>
<td>0/13</td>
<td>0/9</td>
<td>0/10</td>
<td></td>
</tr>
</tbody>
</table>
Neoplastic Nodule Classification – Included non-neoplastic observations

- Hepatocellular neoplasia classification has changed
- "Neoplastic nodules"
  - Would be classified differently (after 1986)
  - Old term: "Hepatocellular neoplastic nodule"
  - New terms for same observations:
    - Hepatocellular hyperplasia
    - Hepatocellular adenoma
- Reevaluation would substantially alter the adenoma classifications
- Freudenthal & Henrich (2000) reference to "hepatocellular adenomas" not appropriate
  - Not known how many "neoplastic nodules" were, in fact, neoplastic.
MTD Exceeded

- MTD significantly exceeded
- Resulted in spurious findings.
- Body weights down > 20%
  - High dose
  - Both males and females
- Mortality significantly higher - > 38%
  - High dose
  - Males
- In Sprague-Dawley CD rats, this level of toxicity typically exacerbates already high level of hepatocellular and other neoplasia
TDCPP
Metabolism Summary

(From Fabian & Landsiedel, 2009; Lynn et al., 1991; Nomeir et al., 1981)
(“GSH” is glutathione. “GS-“ is glutathione conjugate attachment.)

Very rapid conjugation

Slower hydroxylation

“Tris” to “Bis”

Excretion (Urine and Feces)

Excretion (Unidentified polar compounds)

Further metabolized (Exhaled as CO₂)