# TDCPP: Assessment of Evidence Using CIC's "Known to the State to Cause Cancer" Under Proposition 65

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on behalf of
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# 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

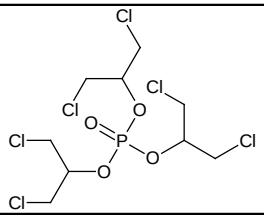
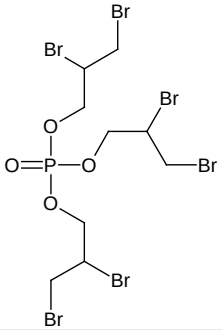
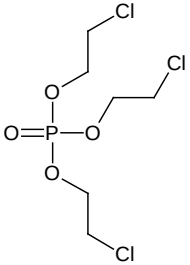
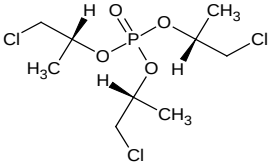
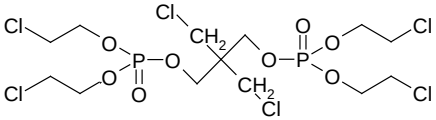
CIC specifies that a single study in one species might be considered sufficient:

- “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)

## STRUCTURES OF TDCPP AND STURCTURALLY SIMILAR COMPOUNDS

| *Substance name* | *CASRN* | *Structure* |
|---|---|---|
| Tris(1,3-dichloro-2-propyl) phosphate (TDCPP) | 13674-87-8 |  |
| Tris(2,3-dibromopropyl) phosphate (TDBPP) | 126-72-7 |  |
| Tris(2-chloroethyl) phosphate (TCEP) | 115-96-8 |  |
| Tris(1-chloro-2-propyl) phosphate (TCPP) | 13674-84-5 |  |
| 2,2-bis(chloroethyl)trimethylene bis[bis(2-chloroethyl)phosphate (V6) | 38051-10-4 |  |

# 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)

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

* 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)

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

* 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)

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

* 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)

| Organ | Tumor | 0 mg/kg/day | 5 mg/kg/day | 20 mg/kg/day | 80 mg/kg/day | Comment |
|---|---|---|---|---|---|---|
| Liver | Hepatocellular adenoma | 2/45 | 7/48 | 1/48 | 13/46 | Noninvasive lesion originally described as a "nodule" would now be separated into hyperplasia and adenoma |
| | 12 months | 0/15 | 0/12 | 0/13 | 3/14 | |
| | Hepatocellular carcinoma | 1/45 | 2/48 | 3/48 | 7/46# | Increased only at excessive dose level |
| | 12 months | 0/15 | 0/12 | 0/13 | 0/14 | |

# 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)

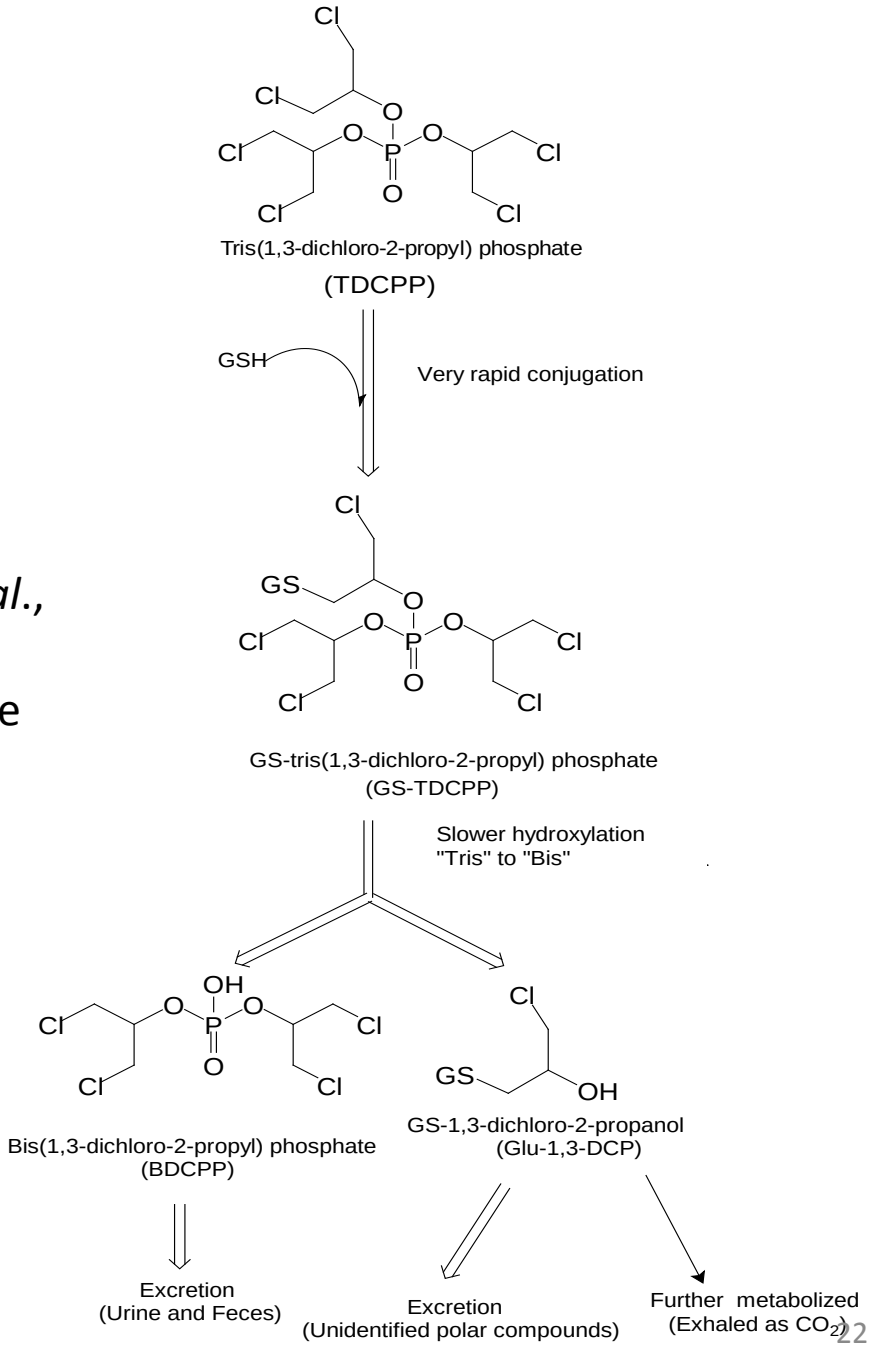
| Organ | Tumor | 0 mg/kg/day | 5 mg/kg/day | 20 mg/kg/day | 80 mg/kg/day | Comment |
|---|---|---|---|---|---|---|
| Liver | Hepatocellular adenoma 12 months | 1/49<br>0/11 | 1/47<br>0/13 | 4/46<br>0/9 | 8/50<br>1/10 | Noninvasive lesion originally described as a “nodule” would now be separated into hyperplasia and adenoma. |
| | Hepatocellular carcinoma 12 months | 0/49<br>0/11 | 2/47<br>0/13 | 2/46<br>0/9 | 4/50<br>0/10 | Not significant increase only at excessive dose level |

# 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.)