Critical Evaluation of OEHHA Documents Pertaining to the Evidence of Carcinogenicity of 3-MCPD and 1,3-DCP

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• 3-Monochloropropane-1,2-Diol
Series of animal cancer studies involving different species, test strains, and routes of administration

• Van Duuren et al, 1974
  – CHR/Ha Swiss Mice, F, dermal, s.c.
  – No significant increase in tumor incidence

• Weisburger et al., 1981
  – Charles River CD rats, M&F, oral gavage
  – No significant increase in tumor incidence
3-MCPD Cancer Studies

- **Sunahara et al., 1993**
  - Fischer 344 rats, M&F, drinking water
  - Leydig-cell adenomas
  - Mammary gland fibroadenoma, M
  - Tubular adenoma, F

- **Cho et al., 2008**
  - Sprague-Dawley rats, M&F, drinking water
  - Leydig-cell tumors
  - Tubular adenoma (F)
  - Tubular carcinoma (M)

- **Jeong et al., 2010 (new)**
  - B6C3F1 mice, M&F, drinking water
  - No significant increase in tumor incidence
3-MCPD and Kidney Tumors

OEHHA report

• Increased incidence of malignant, and benign and malignant kidney tumors in male Sprague-Dawley rats and combined benign and malignant kidney tumors in female Sprague-Dawley rats; kidney tumors are rare in this strain of rat; in males the tumors appeared early;

• Increased incidence of benign kidney tumors in male and female Fischer 344 rats; and

• Increased incidences of renal tubular hyperplasia and exacerbated chronic progressive nephropathy (CPN) in male and female Sprague-Dawley and Fischer 344 rats
OEHHA report

• In male Fischer 344 rats, 3-MCPD significantly increased the incidence of benign and malignant mammary tumors, which are uncommon tumors in this rat strain; and

• 3-MCPD also increased glandular hyperplasia in the male Fischer rat
OEHHA report

- Increased the incidence of benign and malignant Leydig-cell tumors in male Fischer 344 rats, and Leydig-cell tumors (*not specified whether benign or malignant*) in male Sprague-Dawley rats, in which Leydig-cell tumors are uncommon.
### Summary of Tumor Types (Benign and Malignant) – 3-MCPD Oral Studies

<table>
<thead>
<tr>
<th>Species</th>
<th>Mice&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Rats&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Rats&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Rats&lt;sup&gt;4&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Strain</td>
<td>B6C3F1</td>
<td>Charles River CD</td>
<td>Fischer 344</td>
<td>Sprague-Dawley</td>
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<tr>
<td>Sex</td>
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<td>Tumor Types</td>
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<td>Testes</td>
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<td>Leydig-cell Adenoma</td>
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<td>Leydig-cell Carcinoma*</td>
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<td>X (↑)</td>
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<td>Leydig-cell Tumors</td>
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<td>Mammary Gland</td>
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<td>Fibroadenoma</td>
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<td>Adenoma</td>
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<td></td>
<td>Adenocarcinoma*</td>
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<td>Kidneys</td>
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<td>Tubular Adenoma</td>
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<td>Tubular Carcinoma*</td>
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<td>Tubular Adenoma or Carcinoma*</td>
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<td>X (↑)</td>
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</tbody>
</table>
Data do not support 3-MCPD to be a clear human carcinogen

- 3-MCPD was not tumorigenic in mice via, dermal, s.c. or oral exposure
- Malignant kidneys tumors observed in rats in only one of 3 studies and at high dose; response secondary to CPN and renal tubular hyperplasia
- Mammary tumor benign only, in a single rat strain, and not observed in females or other rat strains
- Leydig-cell tumors in rats not well predictive of carcinogenic potential to humans
Data do not support 3-MCPD to be a clear human carcinogen

- Genotoxic response observed within *in vitro* assays not confirmed *in vivo*
- Negative in recent comet assays
- In the *in vitro* test systems, particularly involving bacterial cells, 3-MCPD is metabolized to genotoxic intermediates (glycidol),
- *In vivo*, 3-MCPD is excreted in the urine primary as β-chlorlacetic acid resulting from a different pathway than that involved in the production of glycidol, or is conjugated with glutathione forming a mercapturic acid derivative
3-MCPD - Conclusion

• A chemical would be identified for listing if the weight of scientific evidence clearly shows that it causes invasive cancer in animals, but not if the cancer is the result of a mechanism of action that is not relevant to humans.

• Tumors observed in rats occurred *via* mechanisms of action that are or may be specific to the rat and bear little relevance in an assessment of human risk.

• Furthermore, not all tumor types were identified consistently among the studies and among different strains of rats.
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• Furthermore, not all tumor types were identified consistently among the studies and among different strains of rats.
Therefore, based on a collective review of the available data related to the potential carcinogenicity of 3-MCPD and the limited relevance to humans of the underlying mechanisms of action, the weight of evidence for 3-MCPD does not rise to the “clear showing” that is required for listing decisions, and thus, 3-MCPD should not be included on the ‘Proposition 65’ list.
• 1,3-Dichloro-2-Propanol
One unpublished oral drinking water study in Wistar rats

Benign, malignant, and/or combined benign and malignant tumors of the liver, kidney, tongue, thyroid were observed
1,3-DCP and Liver Tumors

OEHHA Report

• 1,3-DCP significantly increased the incidence of malignant, and benign and malignant liver tumors in male and female rats, the incidence of which was low in untreated controls; and

• In females, 25% of the malignant liver tumors metastasized to the lungs
OEHHA report

- 1,3-DCP significantly increased the incidence of benign and malignant kidney tumors in males, with no kidney tumors observed in untreated controls
OEHHA report

- 1,3-DCP significantly increased the incidence of malignant tongue tumors in males and malignant and benign tumors in males and females; and
- Tongue tumors are rare in Wistar KFM-Han rats
1,3-DCP and Thyroid Tumors

OEHHA report

• 1,3-DCP increased the incidence of benign and malignant thyroid tumors in high-dose male rats

• A significant dose-related trend was observed in adenomas in 1,3-DCP-treated males and in the combined incidence in adenomas and carcinomas in 1,3-DCP-treated males and females

• No thyroid tumors were observed in control males and only 1 benign tumor was observed in control females
Data do not support 1,3-DCP to be a clear human carcinogen

- Only a single study available assessing carcinogenic potential
- No studies in other laboratory species or strains of rats to confirm result
- Findings statistically significant at high dose
- *In vivo* (whole animal) genotoxicity assays were negative
- Given the likely rapid conjugation and detoxification of any mutagenic metabolites of 1,3-DCP *in vivo*, there is no conclusive evidence at the present for a genotoxic mechanism of action
Data do not support 1,3-DCP to be a clear human carcinogen

- Kidney tumors may be secondary to sustained cell proliferation resulting from CPN
- Small increase in thyroid tumors may be due to sustained cell proliferation if not chance
- Tongue tumors may be result of chronic irritation
- Liver tumors may be due to metabolic disturbances – glutathione depletion by metabolite 1,3-dichloroacetone
• The potential carcinogenicity of 1,3-DCP has been evaluated under the conditions of only one single 2-year rat study and no additional studies in other animal species or strains of rat are available to corroborate the results of this study. This, in combination with the fact that the mechanisms of action responsible for the tumors observed may be non-genotoxic, raises doubts regarding the potential carcinogenicity of 1,3-DCP in humans. The weight of evidence, therefore, does not rise to the “clear showing” that is required for listing decisions.