The chemicals listed in Tables A and B below meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

For reproductive toxicity, the U.S. Environmental Protection Agency (U.S. EPA), U.S. National Institute of Occupational Safety and Health (NIOSH), International Agency for Research on Cancer (IARC; for transplacental carcinogenicity only) and Food and Drug Administration (FDA) are authoritative bodies. For carcinogenicity, the authoritative bodies are U.S. EPA, IARC, FDA, NIOSH and the National Toxicology Program (NTP). Chemicals which have been identified as causing cancer or reproductive toxicity are given in the tables below. OEHHA has found that these chemicals have been “formally identified” as causing cancer or reproductive toxicity according to the regulations covering this issue (22 CCR 12306[d]). The chemicals below are the subject of reports published by the authoritative bodies which conclude that the chemicals cause cancer or reproductive toxicity or have been included on a list of chemicals causing these effects issued by the authoritative body. Also, the documents specifically and accurately identify the chemicals and the documents meet one or more of the criteria outlined in 22 CCR 12306 (d)(2).

OEHHA also finds that the criteria given in regulation for “as causing cancer” (22 CCR 12306[e]) or “as causing reproductive toxicity” (22 CCR 12306[g]) have been satisfied for the chemicals in the tables below. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative bodies in making their findings that the specified chemicals cause such effects. A brief discussion of the relevant carcinogenesis and reproductive toxicity studies providing evidence for the findings is presented below. The statements in bold reflect data and conclusions that satisfy the criteria for the sufficiency of evidence for carcinogenicity (22 CCR 12306[e]) or reproductive toxicity (22 CCR 12306[g]).
Table A. Chemicals Meeting the Criteria for Listing as Carcinogens

<table>
<thead>
<tr>
<th>Chemical</th>
<th>CAS No.</th>
<th>Chemical Use</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxythioquinox</td>
<td>2439-01-2</td>
<td>Insecticide and fungicide used on apples, apricots, citrus, pears; walnuts.</td>
<td>U.S. EPA (1996a)</td>
</tr>
<tr>
<td>Primidone</td>
<td>125-33-7</td>
<td>Anti-epileptic drug (phenobarbital analogue).</td>
<td>NTP (1996a, 1996b)</td>
</tr>
<tr>
<td>Thiodicarb</td>
<td>59669-26-0</td>
<td>Carbamate insecticide used on cotton, soybeans, corn, broccoli, cabbage, leafy vegetables, and tomatoes.</td>
<td>U.S. EPA (1996b)</td>
</tr>
<tr>
<td>Vinclozolin</td>
<td>50471-44-8</td>
<td>Fungicide used on various flowers, vegetables, berries and stone fruit to control molds.</td>
<td>U.S. EPA (1996c)</td>
</tr>
</tbody>
</table>

Table B. Chemicals Meeting the Criteria for Listing as Causing Reproductive Toxicity

<table>
<thead>
<tr>
<th>Chemical</th>
<th>CAS No.</th>
<th>Toxicological Endpoints</th>
<th>Chemical Use</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-Dinitrotoluene</td>
<td>121-14-2</td>
<td>male reproductive toxicity</td>
<td>Used in organic synthesis and manufacture of dyes and explosives</td>
<td>U.S. EPA (1986a)</td>
</tr>
<tr>
<td>2,6-Dinitrotoluene</td>
<td>606-20-2</td>
<td>male reproductive toxicity</td>
<td>Used in organic synthesis, manufacture of dyes and explosives</td>
<td>NIOSH (1985) U.S. EPA (1986a)</td>
</tr>
<tr>
<td>Technical Grade Dinitrotoluene</td>
<td>---</td>
<td>female reproductive toxicity, male reproductive toxicity</td>
<td>Used in organic synthesis and manufacture of dyes and explosives</td>
<td>NIOSH (1985)</td>
</tr>
<tr>
<td>Methyl chloride</td>
<td>74-87-3</td>
<td>developmental toxicity, male reproductive toxicity</td>
<td>Used in manufacturing of silicones and other chemical products</td>
<td>NIOSH (1984, 1994)</td>
</tr>
</tbody>
</table>
CARCINOGENS

Oxythioquinox (CAS No. 2439-01-2)

Increased incidence of combined malignant and benign tumors in male mice and at multiple sites in female rats, including rare kidney tumors in female rats.

U.S. EPA (1996a) has classified oxythioquinox as a B2 carcinogen based on sufficient evidence in animals. Exposure to oxythioquinox resulted in lung tumors in male NMRI mice, hepatocellular tumors in both sexes of F344 rats and rare kidney tumors in female F344 rats. The relevant studies are described below.

In one study oxythioquinox was administered to male and female NMRI mice via diet for 91 weeks. In male mice, there was a statistically significant increase in the incidence of alveolar/bronchiolar adenomas (6/59, 11/69, 16/67, 16/69 for control, low-, mid- and high-dose animals, respectively) and in alveolar/bronchiolar adenomas or carcinomas combined (18/60, 24/69, 30/67, 32/69). In female mice, the incidences of alveolar/bronchiolar carcinomas (3/40, 4/36, 4/27, 10/33) and combined carcinomas and adenomas (7/68, 10/69, 8/59, 15/66) were significantly increased in high-dose animals compared to controls. Due to high mortality, the doses in the mid- and high-dose groups were considered by the Agency to be excessive in female mice.

In a second study oxythioquinox was administered to male and female Charles River Fischer 344 rats via diet for two years. In males, there was a statistically significant increase in the incidence of hepatocellular adenomas in the high-dose group (0/50, 0/50, 3/49, 7/50 for control, low-, mid- and high-dose groups, respectively). In females, incidences of liver adenomas or carcinomas (combined) were significantly greater in high-dose animals compared to controls (0/48, 1/46, 3/56, 11/46). Incidences at the high doses exceeded historical control ranges for both males and females. Additionally, there was a statistically significant increase in kidney tubular epithelial neoplasms in high-dose females (combined adenomas/carcinomas: 0/48, 0/46, 4/46, 5/46). Although the increase was only marginally statistically significant (p = 0.054) at the mid-dose, U.S. EPA (1996a) considered it biologically significant. The tumor type is regarded as rare. The Agency concluded that the highest dose in this study may have been slightly excessive, but noted there was no effect on survival. The Agency also noted that kidney tumors, considered to be rare, exceeded the historical control incidence at both the mid- and high-doses.

Primidone (CAS No. 125-33-7)

Increased incidence to an unusual degree of malignant liver tumors, including rare hepatoblastomas in male and female mice.

NTP (1996a; 1996b) has concluded that there is clear evidence of the carcinogenicity of primidone in male and female B6C3F1 mice based on increased incidences of hepatocellular
neoplasms in males and females. An increased incidence in thyroid gland follicular cell adenomas in males was also considered to be chemical related.

NTP (1996a) administered primidone to F344/N rats and B6C3F1 mice in feed for two years. In both male and female mice, marked increases in the incidence of hepatocellular neoplasms were observed. In female mice, there were statistically significant increases in the incidences of hepatocellular adenoma and hepatocellular carcinoma in each dose group. The incidence of hepatocellular carcinoma/hepatoblastoma (combined) was 4/50, 12/50, 20/40, 39/50 for control, low-, mid- and high-dose groups, respectively. The combined incidence of hepatocellular adenoma/carcinoma/hepatoblastoma was 16/50, 42/50, 46/49, 50/50. In male mice, the incidences of hepatocellular adenoma, carcinoma and hepatoblastoma were also significantly greater for each dose group in comparison to controls (combined incidence of hepatocellular carcinoma/hepatoblastoma: 12/50, 39/50, 40/50, 39/50; combined incidence of hepatocellular adenoma/carcinoma/hepatoblastoma: 31/50, 49/50, 49/50, 46/50). There was also a statistically significant increase in thyroid follicular cell adenoma in high-dose male mice (0/49, 3/48, 3/50, 6/50).

No evidence of carcinogenic activity of primidone was found in female rats, but NTP concluded that there was equivocal evidence in male rats based on a marginal increase in thyroid gland follicular cell neoplasms (primarily adenomas) and a marginal increase in renal tubule neoplasms.

These findings were published in a draft technical report and were subsequently reviewed by an external advisory committee in a public meeting and accepted at the December 11-12, 1996 NTP Technical Reports Review Subcommittee Meeting, as reported in the Summary Minutes for that meeting (NTP, 1996b).

Thiodicarb (CAS No. 59669-26-0)

Increased incidence of combined malignant and benign tumors in male rats, female mice and, to an unusual degree, in male mice.

U.S. EPA (1996b) has classified thiodicarb as a Group B2 carcinogen based on statistically significant increases in hepatocellular adenomas, carcinomas and combined adenoma/carcinoma in both sexes of the CD-1 mouse and statistically significant increases in testicular interstitial cell tumors in male Sprague-Dawley rats. The relevant studies are described below.

In the mouse study, CD-1 mice were administered thiodicarb for 97 weeks via diet. The combined incidence of hepatocellular adenoma/carcinoma in males was 8/44, 7/46, 14/49, 37/49 for control, low-, mid- and high-dose groups, respectively. In females, the incidence (of combined hepatocellular adenoma/carcinoma) was 1/48, 1/47, 3/45, 28/49. U.S. EPA (1996b) noted that the highest dose may have been excessive based on effects on the hematopoietic system and other signs of toxicity. Mortality was also increased in female
mice. However, the Agency also noted there were adequate numbers of mice of both sexes available at the study termination to assess the carcinogenicity of thiodicarb. It was further noted that the overall dose selection was improper in that the highest dose was more than 10-fold that of the mid-dose; that there was a suggestive tumor response in the male mouse liver even at the mid-dose (considered inadequate for assessing the carcinogenicity of thiodicarb by the Agency); and that the tumor incidences were unusually high.

In the rat study, thiodicarb was administered to male and female Sprague-Dawley rats via diet for 104 weeks. There was a statistically significant increase in testicular interstitial cell tumors in high-dose males (5/49, 3/48, 3/48, 12/47). No effects were observed in female rats.

Vinclozolin (CAS No. 50471-44-8)

Increased incidence of combined malignant and benign tumors in multiple studies in male and female rats.

U.S. EPA (1996c) has classified vinclozolin as a B2 carcinogen based on sufficient evidence in animals. Exposure to vinclozolin resulted in an increased incidence of testicular Leydig cell tumors (adenomas and carcinomas) and prostate adenomas in male rats and adrenal tumors (adenomas and carcinomas), ovarian adenomas and uterine carcinomas in female rats. The relevant studies are described below.

In its evaluation, U.S. EPA (1996c) looked at one mouse study and two rat studies. In the mouse study, there was a significant increase in hepatocellular neoplasms in both sexes of the C57 mouse at the highest dose level. However, this dose level was considered excessively toxic, based on body weight gain reductions, leading the Agency to question the relevancy of the hepatocellular tumors in the mice.

In a 24-month carcinogenicity study in Wistar rats, statistically significant increases in the incidence of testicular Leydig cell tumors were observed at both mid- and high-doses (combined malignant and benign: 23/48, 25/49, 47/50, 49/50 for control, low-, mid- and high dose groups, respectively; malignant: 0/48, 0/49, 0/50, 2/50). There were also significant increases in prostate adenomas (0/48, 3/49, 7/50, 5/50) in both mid- and high-dose groups, and a significant increasing trend in liver adenomas (0/48, 1/49, 1/50, 3/50). In female rats, increases in benign ovarian sex cord stromal tumors occurred at all doses (4/39, 7/36, 10/45, 29/45). These increases were statistically significant for the high-dose group and of borderline significance for mid-dose animals (p=0.053). Historical control data from 1300 female Wistar rats indicates that this is an uncommon tumor (mean: 0.4% with a range of 0 to 2.0%). There were also increases in uterine adenocarcinoma (1/41, 0/27, 1/27, 7/47) and adrenal cortical malignant and benign tumors (1/42, 2/42, 1/47, 22/48) at the highest dose. U.S. EPA (1996c) considered the highest dose in this study to be excessive and used mid-dose for assessing carcinogenicity. At the mid-dose level, U.S. EPA (1996d) found that vinclozolin exposure resulted in statistically significant increases in Leydig cell tumors (malignant and benign) and prostate adenomas in male rats and benign ovarian sex cord
stromal tumors in female rats. It should be noted that U.S. EPA (1996d), in concluding that vinclozolin induces cancer in animals, also took into account the induction of uterine carcinomas in female Wistar rats.

U.S. EPA (1996c) also evaluated a 24-month chronic feeding study in Wistar rats. In this study, statistically significant increases in Leydig cell malignant and benign tumors occurred in male rats (11/20, 12/20, 17/20, 19/20, 20/20 for controls and 4 dose groups, respectively). There were also significant increases in hepatocellular carcinoma in high-dose males, and a statistically significant positive trend with increasing dose (0/20, 0/20, 1/20, 1/20, 9/20). In females adrenal cortical adenomas and carcinomas (combined) were increased (0/20, 0/20, 0/20, 1/20, 6/20), as were benign ovarian sex cord tumors (0/20, 0/20, 2/20, 4/20, 10/20). For this study U.S. EPA (1996c) also considered the highest dose excessively toxic and used the next highest dose for assessing carcinogenicity.

U.S. EPA (1996c) also noted that vinclozolin and/or its metabolites are structurally related to several pesticides and drugs (and/or their metabolites) that also cause Leydig cell hyperplasia/tumors and ovarian tumors.

**REPRODUCTIVE TOXICANTS**

2,4-Dinitrotoluene (CAS No. 121-14-2); 2,6-Dinitrotoluene (CAS No. 606-20-2); Technical Grade Dinitrotoluene (TDNT)

*Male reproductive toxicity* has been manifested as testicular atrophy and decreased spermatogenesis in experimental animals exposed to TDNT, 2,4-DNT, or 2,6-DNT. *Female reproductive toxicity* has been manifested as non-functioning ovaries in mice exposed to TDNT.

The National Institute for Occupational Safety and Health (NIOSH, 1985) concluded that: “Data from animal studies using TDNT or 2,6-DNT which show reduced spermatogenesis, aspermatogenesis, or testicular atrophy in exposed dogs, rats, and mice and nonfunctioning ovaries in TDNT-exposed mice indicate a potential for adverse reproductive effects from exposure to these compounds.” The Agency's recommendations include the statement that, "...a reproductive hazard may exist for workers exposed to TDNT or 2,6-DNT. Testicular atrophy, decreased spermatogenesis, or aspermatogenesis seen in three species of experimental animals exposed to TDNT or 2,6-DNT and nonfunctioning ovaries in mice exposed to TDNT form the basis for this concern.".

In the Executive Summary of *the Health and Environmental Effects Profile for Dinitrotoluene*, U.S. EPA (1986a), stated that, "An assessment of the data generated by genetic and reproductive toxicity studies suggest that while 2,4- and 2,6-DNT can produce testicular damage, they do not appear to be genetically active in male germ cells. … Chronic and subchronic toxicity studies have revealed that the blood, liver, testis, and neuromuscular
system are the primary organs affected by the DNTs." In reaching this conclusion, the Agency reviewed and summarized published studies demonstrating the adverse effects of 2,4- and 2,6- DNT on reproductive parameters in rats, mice, and dogs.

**Heptachlor (CAS No. 76-44-8)**

**Developmental toxicity** has been manifested in experimental animals as reduced offspring viability.

U.S. EPA (1980) concluded, "Heptachlor has been shown to exhibit numerous toxicological effects in animal systems. …oral doses of heptachlor caused dominant lethal changes in male rats as demonstrated by an increase in the number of resorbed fetuses in intact pregnant rats. Heptachlor administered to rats caused a marked decrease in litter size, both in several litters of one generation as well as in successive generations." U.S. EPA (1986b) concluded that, "A data gap exists in the area of teratology toxicity testing," but that, "Several reproduction studies have been reviewed by the Agency and were adequate to set a NOEL of 1.0 ppm for reproductive effects to the young, the liver being the target organ of effect. No further testing is required."

**Methyl chloride (CAS No. 74-87-3)**

**Male reproductive toxicity** has been manifested in experimental animals as degeneration and atrophy of the seminiferous tubules.  
**Developmental toxicity** has been manifested as morphological abnormalities in experimental animals.

NIOSH (1984) concluded that: "Methyl chloride has been tested in mice and found to be a teratogen. Based on this evidence, NIOSH recommends…that methyl chloride be considered a potential occupational teratogen." NIOSH (1984) also stated that "…methyl chloride induced degeneration and atrophy of the seminiferous tubules in treated male rats." Methyl chloride is also identified as causing teratogenic and adverse reproductive effects in the 'NIOSH Pocket Guide to Chemical Hazards' (NIOSH, 1994).
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National Toxicology Program (NTP, 1996b). *Summary Minutes from Peer Review of Draft Technical Reports of Long-Term Toxicology and Carcinogenesis Studies by the Technical Reports Review Subcommittee on December 11-12, 1996.* NTP, Research Triangle Park, NC.


March 19, 1999
Notice of Intent to List
Package 6a