

**CHEMICALS MEETING THE CRITERIA FOR LISTING AS CAUSING
CANCER VIA THE AUTHORITATIVE BODIES MECHANISM:
CARBARYL AND SPIRODICLOFEN**

PACKAGE 34

November 2009

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Carbaryl and spirodiclofen meet the criteria for listing as known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Health and Safety Code Section 25249.5 *et seq.*), more commonly known as Proposition 65, via the authoritative bodies mechanism. The regulatory requirements for listing by this mechanism are set forth in Title 27, California Code of Regulations, section 25306¹. The regulations include the criteria for evaluating the documentation and scientific findings by the authoritative body that the Office of Environmental Health Hazard Assessment (OEHHA) uses to determine whether listing under Proposition 65 is required.

The U.S. Environmental Protection Agency (U.S. EPA) is one of five institutions that have been identified as an authoritative body for identification of chemicals as causing cancer for the purposes of Proposition 65 (Section 25306[1]). U.S. EPA has identified carbaryl and spirodiclofen as causing cancer. OEHHA has found that carbaryl and spirodiclofen are “formally identified” as causing cancer as required by Section 25306(d). Carbaryl and spirodiclofen are the subject of reports published by the U.S. EPA that conclude that the chemicals cause cancer. Also, U.S. EPA documents specifically and accurately identify the chemicals. These documents meet one or more of the criteria in Section 25306(d)(2).

OEHHA also finds that the criteria for “as causing cancer” in Section 25306(e) have been satisfied for carbaryl and spirodiclofen. In making these determinations, OEHHA relied upon the discussions of data by U.S. EPA in making its findings that carbaryl and spirodiclofen cause cancer. A brief discussion of the relevant carcinogenesis studies providing the scientific evidence supporting U.S. EPA’s findings is presented below for each chemical. The statement in bold reflects data and conclusions that satisfy the criteria for the sufficiency of evidence of carcinogenicity in Section 25306(e). The full citations for the U.S. EPA documents are given in this report.

¹ Formerly Title 22, California Code of Regulations, section 12306. All further references are to Title 27 of the California Code of Regulations unless otherwise indicated.

Chemicals Meeting the Criteria for Listing as Known to the State to Cause Cancer

| Chemical | CAS No. | Chemical Use | Reference |
|---------------|-------------|---|-------------------------------|
| Carbaryl | 63-25-2 | N-methyl carbamate pesticide used on fruit and nut trees, vegetables and grain products; lawns, plants and shrubs; for landscape maintenance and pet care (e.g., pet collars, powders). | U.S. EPA (2002; 2007a; 2007b) |
| Spirodiclofen | 148477-71-8 | Miticide used on citrus, pome fruit, stone fruit, and tree nuts. | U.S. EPA (2004a) |

Carbaryl (CAS No. 63-25-2)

Increased incidence of malignant and combined malignant and benign tumors in male mice and increased incidence of malignant tumors in male rats.

U.S. EPA (2002) has concluded that carbaryl is “likely to be carcinogenic to humans” based on increased incidences of hemangiosarcoma in male mice and urinary bladder transitional cell tumors in male rats. Previously, carbaryl had been classified as a Group C, possible human carcinogen (U.S. EPA, 1994). U.S. EPA (2002) reclassified carbaryl to “likely to be carcinogenic to humans” after the tumor data from both the mouse and rat cancer bioassays had been re-evaluated. The 2002 classification was reconfirmed in U.S. EPA’s Reregistration Eligibility Decision Document for Carbaryl (U.S. EPA, 2007a; 2007b). U.S. EPA (2002) based its classification on the studies summarized below.

CD-1 mice were exposed to carbaryl via diet for 24 months. In males, the incidence of hemangiosarcoma (1/66, 7/66, 8/69, and 8/68 for control, low-, mid- and high-dose groups, respectively) was statistically significantly [$p < 0.05$] increased at all dose levels, and the incidence of combined hemangioma and hemangiosarcoma (2/66, 7/66, 10/69 and 10/68) was significantly increased for the two highest dose groups [$p < 0.05$]. The incidence of hemangiosarcoma (12%) in the two highest dose groups exceeded the historical control range for data for hemangiosarcomas in the liver [0-8%] and spleen [0-4.2%] from a number of laboratories, as submitted by the registrant. In addition, the incidences of renal tubule cell adenoma (0/66, 0/66, 0/69, and 3/68), carcinoma (0/66, 0/66, 1/69 and 3/68) and combined renal tubule cell adenoma and/or carcinoma (0/66, 0/66, 1/69 and 6/68 [$p < 0.05$]) were increased in high-dose males. However, U.S. EPA considered the high dose excessive for carcinogenicity assessment.

In female mice, the incidences of hemangiosarcomas (2/63, 4/70, 3/66, and 9/61 [$p < 0.05$]) and combined hemangioma and/or hemangiosarcoma was also increased (4/63, 4/70, 4/66 and 9/61). Although these incidences occurred at doses considered excessive,

U.S. EPA (2002) concluded that the findings were supportive of the vascular tumors in male mice.

Sprague-Dawley rats were exposed to carbaryl via diet for 104 weeks. Statistically significant increases in urinary bladder transitional cell papilloma, carcinoma and combined papilloma and carcinoma were observed in high dose animals of both sexes. In males, the incidence of urinary bladder transitional cell papilloma was 0/66, 0/66, 0/68 and 14/68 for control, low-, mid- and high-dose groups, respectively; the incidence of urinary bladder transitional cell carcinoma was 0/66, 0/66, 0/68, and 10/68 [$p < 0.01$] and the incidence of papilloma and carcinoma combined was 0/66, 0/66, 0/68, and 24/68 [$p < 0.01$]. The incidences exceeded historical control ranges in male Sprague-Dawley rats for urinary bladder transitional cell papilloma (0-1.1%) and carcinoma (0-1.4%) in 27 studies at the conducting laboratory. In addition, thyroid follicular cell adenoma (0/66, 2/66, 0/68 and 9/68) and combined thyroid follicular cell adenoma and carcinoma (0/66, 2/66, 1/68, and 9/68) were significantly increased [$p < 0.01$] in high-dose male rats.

In female rats, the incidences of urinary bladder transitional cell papilloma (1/86, 0/79, 0/77, and 8/86 [$p < 0.05$]), carcinoma (0/86, 0/79, 0/77, and 5/86 [$p < 0.05$]) and combined papilloma and carcinoma (1/86, 0/79, 0/77, and 13/86 [$p < 0.01$]) were significantly increased in high dose animals. In addition, female rats had increased incidences of hepatocellular adenomas (1/54, 0/56, 3/61, and 7/65 [$p < 0.05$]). These incidences exceeded the historical control ranges for urinary bladder papillomas (0-1.4%) and carcinomas (none reported) and hepatocellular adenomas (0-6.3%) in female Sprague-Dawley rats in 27 studies from the conducting laboratory.

U.S. EPA concluded that the high dose in these studies in Sprague-Dawley rats was excessive for carcinogenicity testing, but that the mid-dose was too low to adequately test the carcinogenic potential of carbaryl. Re-examination of histopathology slides from animals sacrificed at week 53 of the study found that mid-dose males and high-dose males and females had preneoplastic bladder lesions, namely urinary bladder transitional cell hyperplasia. The presence of preneoplastic lesions at week 53 at a dose below adequate for carcinogenicity testing led U.S. EPA (2002) to conclude that had the mid-dose been adequate for carcinogenicity assessment, bladder tumors seen at the high dose may have occurred at the mid-dose as well.

U.S. EPA noted that carbaryl was found to be clastogenic in *in vitro* studies with effects on chromosomal aberrations and aneuploidy; one report suggested that carbaryl may induce oxidative stress. U.S. EPA (2002) wrote that "These types of effects may contribute to carbaryl-induced tumors." U.S. EPA (2002) included *in vitro* clastogenicity in its basis for the classification of carbaryl as "Likely to be carcinogenic to humans" in

addition to the statistically significant increase in hemangiosarcomas in male mice (at all doses), statistically significant increases in urinary bladder tumors in male and female rats at a dose considered excessive for carcinogenicity testing and evidence of preneoplastic lesions in the bladder of male rats at a dose that was inadequate to test the carcinogenicity potential of carbaryl.

Spirodiclofen (CAS No. 148477-71-8)

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

U.S. EPA (2004a) has concluded that spirodiclofen is “likely to be carcinogenic to humans.” U.S. EPA’s conclusion was based on an increased incidence of malignant uterine tumors in female rats, testicular adenomas in male rats and combined malignant and benign liver tumors in male and female mice (U.S. EPA, 2004a). The studies evaluated by the U.S. EPA (2004a) are referred to in other U.S. EPA documents (U.S. EPA, 2004b) and are summarized below.

Male and female Wistar rats were exposed to spirodiclofen via diet for two years. In female rats, the incidence of uterine adenocarcinoma (4/47, 5/48, 3/46, 2/46 and 14/47 [$p < 0.01$] for control, low, mid-low, mid-high and high-dose groups, respectively) was significantly increased in high-dose animals and occurred with a positive trend [$p < 0.01$]. The incidence in the high-dose group (30%) far exceeded the historical control incidence from the testing laboratory (range, 2-10%). In male rats, an increase in Leydig cell adenomas (2/34, 1/35, 0/43, 4/35, and 10/43 [$p < 0.05$]) was statistically significant in high-dose animals and occurred with a positive trend [$p < 0.01$].

Male and female CD-1 mice were exposed to 0, 25, 3500 or 7000 ppm spirodiclofen via diet for 18 months. Male mice had statistically significant increases in hepatocellular adenoma (0/46, 0/50, 5/47, and 6/48 [$p < 0.05$] for control, low-, mid- and high-dose groups, respectively) and combined hepatocellular adenoma and/or carcinoma (1/46, 1/50, 8/47 [$p < 0.05$], and 10/48 [$p < 0.01$]) which occurred with positive trends [$p < 0.01$]. The incidence of hepatocellular carcinoma (1/46, 1/50, 3/47, and 5/48) was also increased and occurred with a positive trend [$p < 0.05$]. In female mice, two carcinomas were found in both the mid- and high-dose groups. The incidence of combined hepatocellular adenoma or carcinoma (0/49, 0/50, 5/48 [$p < 0.05$], and 3/47) was significantly increased in mid-dose animals and occurred with a positive trend [$p < 0.05$]. The combined incidence of hepatocellular adenoma and/or carcinoma exceeded historical control ranges provided by the performing laboratory, which were 4-14% in males and 0-2% in females.

REFERENCES

U.S. Environmental Protection Agency (U.S. EPA, 1994). *Memorandum: Carcinogenicity Peer Review of Carbaryl (1-Naphthyl N-methylcarbamate)*. Office of Prevention, Pesticides and Toxic Substances. May 12, 1994.

U.S. Environmental Protection Agency (U.S. EPA, 2002). *Memorandum: Carbaryl – Report of the Cancer Assessment Review Committee*. Health Effects Division. Office of Pesticide Programs. February 12, 2002.

U.S. Environmental Protection Agency (U.S. EPA, 2004a). *Memorandum: Spirodiclofen: Report of the Cancer Assessment Review Committee. PC Code 124871*. Health Effects Division. Office of Pesticide Programs. June 10, 2004.

U.S. Environmental Protection Agency (U.S. EPA, 2004b). *Memorandum: Spirodiclofen: 1st Report of the Hazard Identification Assessment Review Committee*. Health Effects Division. Office of Pesticide Programs. June 16, 2004.

U.S. Environmental Protection Agency (U.S. EPA, 2007a). *Memorandum: Carbaryl. HED Chapter of the Reregistration Eligibility Decision Document (RED). PC Code: 056801, DP Barcode: D334770*. Health Effects Division. Office of Pesticide Programs. June 29, 2007.

U.S. Environmental Protection Agency (U.S. EPA, 2007b). *Reregistration Eligibility Decision for Carbaryl*. Office of Pesticide Programs. September 24, 2007