CHEMICALS MEETING THE CRITERIA FOR LISTING AS CAUSING CANCER VIA THE AUTHORITATIVE BODIES MECHANISM: IPROVALICARB AND PROPOXUR

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The chemicals listed in the table below meet the criteria for listing under Proposition 65[1] via the authoritative bodies listing mechanism as known to the State to cause cancer. The regulatory requirements for listing by this mechanism are set forth in Title 22, California Code of Regulations, Section 12306[2] and 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.

U.S. Environmental Protection Agency (U.S. EPA) is one of five institutions that have been identified as authoritative bodies for identification of chemicals as causing cancer for the purposes of Proposition 65 (§12306(1)). U.S. EPA has identified each of the chemicals in the table below as causing cancer. The Office of Environmental Health Hazard Assessment (OEHHA) has found that these chemicals have been "formally identified" as causing cancer as required by §12306(d). The chemicals below are the subjects of reports published by the authoritative body that conclude that the chemicals cause cancer. Also, the U.S. EPA documents specifically and accurately identify the chemicals, and the documents meet one or more of the criteria outlined in §12306(d)(2).

OEHHA also finds that the criteria given in regulation for "as causing cancer" (§12306(e)) have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative body in making its finding that the specified chemicals cause cancer. A brief discussion of the relevant carcinogenesis studies providing evidence for the findings is presented below. The statements in bold reflects data and conclusions that satisfy the criteria for the sufficiency of evidence for carcinogenicity (§12306(e)). The full citation for the U.S. EPA documents are given in this report.

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5

[2] All further references are to Title 22 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
Iprovalicarb	140923-17-7; 140923-25-7	Fungicide used on imported grapes and raisins. Not registered by U.S. EPA.	U.S. EPA (2002)
Propoxur	114-26-1	Used for the control of various insects such as earwigs, cockroaches, spiders, ants, silverfish and clover mites.	U.S. EPA (1996)

Iprovalicarb (CAS No. 140923-17-7 ;CAS No. 140923-25-7)

Increased incidence of malignant tumors in male and female rats, to an unusual degree with respect to site, and at multiple rare sites in female rats.

U.S. EPA (2002) has concluded that iprovalicarb is "likely to be a human carcinogen" based on the occurrence of rare tumors in male and female rats. The studies considered by U.S. EPA (2002) are briefly described below.

Male and female Wistar rats (50 rats/group/sex) were exposed to iprovalicarb via diet for 24 months. An additional 10 rats/group/sex were exposed to iprovalicarb and sacrificed at 12 months. Two male rats developed osteosarcoma of the femur and one developed osteosarcoma of the lower jaw. The combined incidence of osteosarcomas (0/50, 0/50, 0/49, 3/50 [$p<0.05$]; $p<0.01$ for dose related trend) was significantly greater than that in control animals. In addition, one chondrosarcoma of the nasal cavity was observed in an animal receiving the highest dose of iprovalicarb. U.S. EPA (2002) considered chondrosarcoma and osteosarcoma as having a common etiology but could not combine these tumors for statistical analyses since the nasal cavity of only the one rat with a gross nasal lesion was examined microscopically. Both chondrosarcomas and osteosarcomas are rare malignant tumors. In the historical control data for three substrains of Wistar rats from the performing laboratory, no osteosarcomas or chondrosarcomas were reported in 698 male and 700 female control rats in 14 two-year studies. In additional historical control data submitted by the testing laboratory, one osteosarcoma was found in a control male rat (total number of rats not indicated).

U.S. EPA (2002) concluded that there were also rare tumors at multiple sites in female rats. These included malignant mixed Mullerian tumors of the uterus (0/49, 0/49, 1/48, and 2/48 for control, low-, mid- and high dose groups, respectively) and benign transitional cell papillomas of the urinary bladder (0/49, 0/48, 0/48 and 2/48). Two malignant squamous cell carcinomas of the clitoral gland were observed in two high dose

animals; these two were the only animals examined microscopically for tumors of the clitoral gland. In addition to the above tumors, thyroid follicular cell adenomas (0/49, 0/49, 1/48 and 2/48) and carcinomas (0/49, 0/49, 1/48 and 1/48) were observed. The combined incidence of thyroid follicular cell adenoma or carcinoma (0/49, 0/49, 2/48 and 3/48) occurred with a statistically significant trend ($p<0.05$). Thyroid follicular cell tumors are considered uncommon tumors in female Wistar rats (U.S. EPA, 2002). No treatment related tumors were observed in studies with male or female $B6C3F_1$ mice.

Propoxur (CAS No. 114-26-1)

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

U.S. EPA (1996) has concluded that propoxur is a probable human carcinogen (Group B2). The 1996 evaluation was the fourth U.S. EPA evaluation of propoxur. Propoxur was first classified in Group B2 in 1986 and was re-evaluated in 1990 and again in 1991. In all evaluations, U.S. EPA concluded that propoxur should be classified as a probable human carcinogen. Relevant studies are briefly summarized below.

In studies conducted in 1984, male and female Wistar rats (50 animals/group/sex) were exposed to propoxur via diet for two years. Statistically significant increases in the incidence of papillomas and carcinomas of the urinary bladder were observed in both male and female rats. In male rats, the incidence of bladder carcinomas (0/48, 0/50, 0/49 and 8/49 for control, low-, mid- and high-dose groups, respectively) was significantly greater in the high dose group compared to that in control animals [$p<0.01$]. The combined incidence of bladder papillomas and carcinomas (0/48, 0/50, 1/49 and 33/49) was also significantly greater in the high dose group compared to that in control animals [$p<0.01$]. In female rats, the incidence of bladder carcinomas (0/47, 0/46, 0/47 and 5/48) was significantly greater in the high-dose group than in the control group [$p<0.05$]. The combined incidence of bladder carcinomas and papillomas in female rats was 0/47, 0/46, 0/47, and 33/48 [$p<0.01$]. There was also a significant dose-related trend [$p=0.024$] associated with the incidence of carcinoma of the uterus (3/48, 4/48, 3/47, and 8/47).

U.S. EPA reported in its 1986 evaluation that this increase was associated with early dose-related deaths and that there was an earlier onset of uterine carcinoma in the high dose group (U.S. EPA, 1996).

In a 1988 study, female Wistar rats (70 animals/group) were exposed to propoxur via diet for up to two years. During the two-year period, a considerable number of animals (40 or more/group) were sacrificed. For animals that died between 78 weeks and the final two-year sacrifice or were sacrificed at two years, the combined incidence of urinary bladder papilloma or carcinoma was 0/29, 0/24, 0/29, 0/26, 6/29 [$p=0.0117$], 13/29 [$p<0.001$],

and 10/24 [p<0.001](for control, 50, 250, 1000, 3000, 5000 and 8000 ppm groups, respectively). Uterine carcinomas were reported in two female rats in the highest dose group. Upon re-evaluation, the incidence was found to be 1/17, with the second tumor reclassified as a carcinoma *in situ*.

In studies conducted in 1992, male and female B6C3F_1 mice (50 animals/group/sex) were exposed to propoxur via diet for two years. In male mice, the incidence of hepatocellular adenoma (10/49, 10/49, 15/49 and 21/50, for control, low-, mid- and high-dose animals, respectively) was significantly greater in the high-dose group than in the control group [p<0.05]. The combined incidence of hepatocellular adenoma and carcinoma in male mice was 15/49, 16/49, 23/49, and 26/50 [p<0.05].

REFERENCES

U.S. Environmental Protection Agency (U.S. EPA, 1996). *Memorandum: Carcinogenicity Peer Review of (4th) Baygon (Propoxur).* Office of Prevention, Pesticides and Toxic Substances. June 17, 1996.

U.S. Environmental Protection Agency (U.S. EPA, 2002). Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Iprovalicarb. Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. April 11, 2002.