CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

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The chemicals listed in the table below may 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 25306[1]. These regulations describe the criteria that the Office of Environmental Health Hazard Assessment (OEHHA) uses to evaluate whether listing under Proposition 65 is required.

The U.S. Environmental Protection Agency (U.S. EPA) is one of five institutions identified as an authoritative body for identification of chemicals as causing cancer for the purposes of Proposition 65[2]. OEHHA has found that the chemicals in the table below appear to be "formally identified" by U.S. EPA in its reports as causing cancer pursuant to Section 25306. These chemicals are the subjects of reports published by the U.S. EPA that conclude that the chemicals cause cancer. To reach this conclusion, OEHHA relied upon U.S. EPA's discussion of data and their conclusion that the specified chemicals cause cancer. A brief discussion of the relevant carcinogenesis studies contained in the U.S. EPA's report is presented below. The statements in bold reflect data and conclusions that appear to satisfy the criteria for the sufficiency of evidence for carcinogenicity as required by Section 25306(e). The full citations for the U.S. EPA documents are given at the end of this document.

[1] All further references are to sections of Title 27 (formerly Title 22) of the California Code of Regulations unless otherwise indicated.
[2] Section 25306(l).

Chemicals Under Consideration for Possible 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)
Metam Potassium (Potassium N-methyldithiocarbamate)	137-41-7	Dithiocarbmate soil fumigant used for producing lettuce, potatoes, onions, tomatoes, and watermelon.	U.S. EPA (1995; 2005; 2007c)
Metofluthrin	240494-70-6	Synthetic pyrethroid insecticide used in pest strips and in personal bug repellant devices.	U.S. EPA (2006)
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 a preneoplastic lesion, 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.

Metam potassium [Potassium N-methyldithiocarbamate] (CAS No. 137-41-7)

Increased incidence of malignant tumors in male and female mice.

In 2005 and 2007 memoranda, U.S. EPA states: "Unless further qualified or specified, use of the term 'metam sodium' should be assumed to also include 'metam potassium'." The U.S. EPA (1995) classified metam sodium (sodium N-methyldithiocarbamate, the sodium salt of N-methyldithiocarbamate) as a probable human carcinogen (Group B2) in 1995, and reaffirmed this classification in the 2005 and 2007 memoranda (U.S. EPA, 2005; 2007c). Thus, by reference metam potassium is also classified as a Group B2 probable human carcinogen by the U.S. EPA. The classification is based on statistically significant increases in malignant angiosarcomas in both sexes of the CD-1 mouse, supported by a similar tumor type in male Wistar rats (malignant hemangiosarcomas). U.S. EPA identified methyldithiocarbamate salts (metam sodium, metam potassium) in its new Reregistration Eligibility Decision (RED) document for these chemicals (U.S. EPA, 2008). Both metam sodium and metam potassium are water soluble, and water soluble dithiocarbamate salts dissociate to their respective ions (WHO, 1988). [Both N-methyldithiocarbamate salts undergo rapid hydrolysis in the environment and in biological organisms to yield methyl isothiocyanate.]

Metham sodium (metam sodium) was listed as causing cancer under Proposition 65 in 1998. Based on U.S. EPA 2005 and 2007 memoranda, metam potassium also meets the

criteria for listing as causing cancer under Proposition 65. The relevant cancer bioassays are described below.

Metam sodium was administered to male and female CD-1 mice in drinking water for two years. Angiosarcomas were observed in both males and females, with liver and spleen being the primary targets. In male mice, there were statistically significant

increases in angiosarcoma of the liver (1/52, 8/52, 5/55, and 10/52 [$p<0.01$] for control, low-, mid- and high-dose animals, respectively), spleen (6/53, 3/53, 10/55, and 21/53 [$p<0.01$]) and bone marrow [femur] (3/53, 3/53, 8/55, and 15/53 [$p<0.01$]). The combined incidence of angiosarcoma (at all sites) in male mice was 7/52, 12/52, 12/55, and 27/52 [$p<0.01$]. In female mice, the incidence of angiosarcoma of the spleen was significantly increased in mid- and high-dose animals compared to controls (0/55, 2/55, 4/47 [$p<0.05$], and 5/52 [$p<0.05$]). The incidence of angiosarcoma of the liver was also increased (0/54, 0/55, 1/47, and 4/52) although the increase was of borderline significance ($p=0.055$).

Metam sodium was administered to male and female Wistar Tox rats in drinking water for two years. In male rats, there was a significant increase in the incidence of hemangiosarcoma, a tumor similar to angiosarcoma, in low- and mid-dose animals (0/47, 3/49 [$p<0.05$], 8/50 [$p<0.01$], 3/51). No effect was seen in female rats.

Metofluthrin (CAS No. 240494-70-6)

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

U.S. EPA (2006) has concluded that metofluthrin is "Likely to be a human carcinogen" based on the occurrence of liver carcinomas and combined liver carcinomas and adenomas in male and female rats. The studies considered by U.S. EPA (2006) are briefly described below.

Male and female Wistar rats were exposed to metofluthrin via diet for 104 weeks. In male rats, there were statistically significant increases in liver carcinomas (0/68, 0/68, 0/69, 3/70, and 8/69 [$p<0.01$], for control, low-, mid-low, mid-high, and high-dose groups, respectively) and combined liver adenomas and/or carcinomas (1/68, 1/68, 3/69, 8/70 [$p<0.05$], and 12/69 [$p<0.01$]). These tumors occurred with significant increasing trends [$p<0.01$]. The incidence of liver adenoma (1/68, 1/68, 3/69, 5/70, and 6/69) also occurred with a significant increasing trend [$p<0.05$].

In female rats, the incidences of liver adenoma (1/38, 1/32, 0/40, 3/38, and 7/46 [p<0.05]), liver carcinoma (0/40, 2/37, 1/42, 2/40 and 7/47 [p<0.05]) and combined liver adenoma and/or carcinoma (1/40, 3/37, 1/42, 5/40 [p<0.04], and 12/47 [p<0.01] were all statistically significantly increased. These tumors occurred with statistically significant increasing trends [p<0.01].

Male and female CD-1 mice were exposed to metofluthrin via diet for 78 weeks. No treatment-related increases in tumor incidence were observed.

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.

The 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, 1995). *Memorandum: Carcinogenicity Peer Review of Metam Sodium.* Office of Prevention, Pesticides and Toxic Substances. May 1, 1995.

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, 2005). *Memorandum: Metam Sodium: Revised HED Human Health Risk Assessment for Phase 3: DP Barcode: D318051, Metam Sodium PC Code: 039003, MITC PC Code: 068103.* Health Effects Division. Office of Pesticide Programs. June 13, 2005.

U.S. Environmental Protection Agency (U.S. EPA, 2006). Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Metofluthrin. PC Code 109709. Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. June 6, 2006.

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.

U.S. Environmental Protection Agency (U.S. EPA, 2007c). *Memorandum: Metam Sodium: Phase 5 Revised Chapter of the Reregistration Eligibility Decision Document (RED); DP Barcode: D337533, Metam Sodium PC Code: 039003; Metam Potassium PC Code: 039002, MITC PC Code: 068103.* Health Effects Division. Office of Pesticide Programs. April 12, 2007.

U.S. Environmental Protection Agency (U.S. EPA, 2008). *Reregistration Eligibility Decision (RED) for Methyldithiocarbamate Salts -Metam Sodium/Potassium and MITC.* Office of Pesticide Programs. July 9, 2008.

World Health Organization (WHO, 1988). *Dithiocarbamate Pesticides, ethylenethiourea and propylenethiourea: a general introduction.* Environmental Health Criteria 78. International Program on Chemical Safety. World Health Organization. Geneva. 1988. Available at URL: http://www.inchem.org/documents/ehc/ehc/ehc78.htm.