CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986 (Proposition 65)

Chemicals Under Consideration For Possible Listing Via The Authoritative Bodies Mechanism: Request For Relevant Information February 15, 2008

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65 or the Act) which is codified at Health and Safety Code section 25249.5 et seq., requires the Governor to publish, and update at least annually, a list of chemicals known to the State to cause cancer or reproductive toxicity. The Act describes the mechanisms for administratively listing chemicals as known to the State to cause cancer or reproductive toxicity (Health and Safety Code section 25249.8.)

One mechanism by which a chemical is listed is if a body considered to be authoritative by the state's qualified experts has formally identified it as causing cancer or reproductive toxicity. For carcinogenicity, the U.S. Environmental Protection Agency (U.S. EPA), the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), the U.S. Food and Drug Administration (FDA), and the National Institute for Occupational Safety and Health (NIOSH) have been identified as authoritative bodies for purposes of the Act. The criteria for listing chemicals through the "authoritative bodies" mechanism are set forth in Title 22, California Code of Regulations, section 12306[1].

As the lead agency for the implementation of Proposition 65, the Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency, is investigating the possible listing of the chemicals identified below, based upon information in the references cited. Documentation summarizing the rationale for considering the evaluation of these chemicals for possible administrative listing is available from OEHHA's Proposition 65 Implementation Office at the address and telephone number indicated below, or from the Internet at the following address: **http://www.oehha.ca.gov/prop65.html**.

OEHHA is committed to public participation and external scientific peer review in its implementation of Proposition 65, and welcomes public input on this listing process. As part of its efforts to ensure that regulatory decisions are based upon a thorough consideration of all relevant information, OEHHA is soliciting information concerning whether the criteria set out in Section 12306 have been met for these chemicals.

A public forum to present oral comments and to discuss the scientific data and other information concerning whether these chemicals meet the criteria for listing set forth in Section 12306 will be scheduled only upon request. Such request must be submitted in writing no later than 30 days before the close of the comment period on **Tuesday, April 15, 2008**. The written request must be sent to OEHHA at the address listed below no later than *Friday, March 14, 2008***.** A notice for the public forum, if one is requested, will be posted on the OEHHA web site at least ten days in advance of the

[1] All further citations are to Title 22 of the California Code of Regulations unless otherwise indicated.

forum date. The notice will provide the date, time, location and subject matter to be heard. Notices will also be sent to those individuals requesting such notification. Written comments provided in **triplicate**, along with supporting information, should be submitted to:

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
Street Address: 1001 I Street
Sacramento, California 95814
Mailing Address: P.O. Box 4010, MS-19B
Sacramento, California 95812-4010
Fax No.: (916) 323-8803
Telephone: (916) 445-6900
Or via email addressed to coshita@oehha.ca.gov

Comments may also be delivered in person or by courier to the above address. It is requested, but not required, that written comments and supporting documentation be transmitted via email addressed to: coshita@oehha.ca.gov. In order to be considered, comments must be received at OEHHA by 5:00 p.m. on Tuesday, April 15, 2008.

Following the review of all comments received, OEHHA will announce its intention to proceed with the listing of the candidate chemicals if they meet the regulatory criteria for administrative listing in a *Notice of Intent to List Chemicals*.

Chemicals which may meet the criteria set forth in Section 12306 for listing as known to cause **cancer** via the "authoritative bodies" mechanism:

Chemical	CAS No.	Chemical Use	U.S. EPA Classification	Reference
Benthiavalicarb -isopropyl[1]	177406-68-7	Fungicide used on tomatoes and grapes.	Likely to be carcinogenic to humans	U.S. EPA (2005a)
Mepanipyrim[1]	110235-47-7	Fungicide used on selected fruits and vegetables (e.g., grapes, strawberries, tomatoes).	Likely to be carcinogenic to humans	U.S. EPA (2004)
Pirimicarb	23103-98-02	Dimethylcarbamate insecticide used on cereals, sugar beets, potatoes, fruits, vegetables.	Likely to be carcinogenic to humans	U.S. EPA (2005b)
Resmethrin	10453-86-8	Pyrethroid pesticide used for insect control for household, greenhouse, industrial, food handling establishments; mosquito control for USDA meat and poultry inspection programs and West-Nile virus.	Likely to be carcinogenic to humans	U.S. EPA (2005c)

[1]Not currently registered in the United States.

REFERENCES

U.S. Environmental Protection Agency (U.S. EPA, 2004). *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Mepanipyrim.* Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. April 20, 2004.

U.S. Environmental Protection Agency (U.S. EPA, 2005a). *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Benthiavalicarb-isopropyl.* Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs. October 18, 2005.

U.S. Environmental Protection Agency (U.S. EPA, 2005b). *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Pirimicarb.* Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. July 13, 2005.

U.S. Environmental Protection Agency (U.S. EPA, 2005c). *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Resmethrin.* Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs. May 25, 2005.

CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

PACKAGE 31a

February 2008

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

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 22, California Code of Regulations, section 12306[1]. 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 which has been identified as an authoritative body for identification of chemicals as causing cancer for the purposes of Proposition 65 (Section 12306(l)). The U.S. EPA has identified each of the chemicals in the table below as causing cancer. OEHHA has found that these chemicals appear to be "formally identified" as causing cancer as defined in Section 12306(d). The chemicals below are the subjects of reports published by U.S. EPA that conclude that the chemicals cause cancer. Also, the documents specifically and accurately identify the chemicals, and the documents meet one or more of the criteria outlined in Section 12306(d)(2).

OEHHA also finds that the criteria for "as causing cancer" in Section 12306(e) appear to have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the discussion of data by the U.S. EPA in making their findings 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 reflect data and conclusions that appear to satisfy the criteria for the sufficiency of evidence for carcinogenicity in Section 12306(e). Full citations for the U.S. EPA documents are given in this report.

[1] All further references are to Title 22 of the California Code of Regulations unless otherwise indicated.

Chemicals Under Consideration for Possible Listing as Known to the State to Cause Cancer

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Benthiavalicarb-isopropyl[1]	177406-68-7	Fungicide used on tomatoes and grapes.	Likely to be carcinogenic to humans	U.S. EPA (2005a)
Mepanipyrim[1]	110235-47-7	Fungicide used on selected fruits and vegetables (e.g., grapes, strawberries, tomatoes).	Likely to be carcinogenic to humans	U.S. EPA (2004)
Pirimicarb	23103-98-02	Dimethylcarbamate insecticide used on cereals, sugar beets, potatoes, fruits, vegetables.	Likely to be carcinogenic to humans	U.S. EPA (2005b)
Resmethrin	10453-86-8	Pyrethroid pesticide used for insect control for household, greenhouse, industrial, food handling establishments; mosquito control for USDA meat and poultry inspection programs and West-Nile virus.	Likely to be carcinogenic to humans	U.S. EPA (2005c)

[1]Not currently registered in the United States.

Benthiavalicarb-isopropyl (CAS No. 177406-68-7)

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

U.S. EPA (2005a) has classified benthiavalicarb-isopropyl as "Likely to be carcinogenic to humans" based on malignant uterine tumors in female rats, malignant liver tumors in male mice and combined malignant and benign liver tumors in male and female mice; liver tumors in male rats and thyroid follicular cell tumors in male mice added some support to this classification. The studies evaluated by U.S. EPA are summarized below.

Male and female Fischer 344 rats (70 animals/group/sex) were exposed to 0, 50, 200, 5000 or 10000 ppm benthiavalicarb-isopropyl via diet for 24 months. In female rats, the incidence of uterine adenocarcinoma (3/70, 3/70, 4/70, 13/70 [$p<0.01$] and 12/70 [$p<0.05$] for control, 50, 200, 5000 and 10000 ppm dose groups, respectively) was significantly greater than that in controls and occurred with a positive trend [$p<0.01$]. In male rats, incidences of hepatocellular adenoma (1/70, 2/70, 2/70, 2/70, and 7/70 [$p<0.05$]) and combined hepatocellular adenoma or carcinoma (1/70, 4/70, 2/70, and 8/70 [$p<0.05$]) were both significantly increased. U.S. EPA (2005a) concluded that these increases provided some supporting evidence of liver tumorigenesis in rats.

Male and female $B6C3F_1$ mice (60 animals/group/sex) were exposed to 0, 20, 100, 2500, or 5000 ppm benthiavalicarb-isopropyl via diet for 104 weeks. U.S. EPA (2005a) concluded that the highest dose was excessively toxic in male mice. The next highest dose was considered adequate for carcinogenicity assessment, and all tumors supporting the cancer classification were considered treatment-related at the two highest doses. In male mice, statistically significant increases in hepatocellular adenoma (15/50, 6/49,

17/47, 43/48 [p<0.01] and 47/49 [p<0.01]), hepatocellular carcinoma (12/60, 12/59, 12/60, 36/60 [p<0.01], and 43/60 [p<0.01]), hepatoblastoma (0/49, 0/46, 0/47, 12/47 [p<0.01], and 9/48 [p<0.01]) and combined hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma (29/60, 19/59, 24/60, 54/60 [p<0.01], and 59/60 [p<0.01]) were observed at the two highest dose groups and occurred with positive trends [p<0.01]. Tumor incidences far exceeded the sponsor reported historical control ranges for male $B6C3F_1$ mice (hepatocellular adenoma, 25-56%; hepatocellular carcinoma, 12-40%; and hepatoblastoma, 0-2%). Additionally, a statistically significant increase in thyroid follicular cell adenoma (0/46, 1/40, 0/40, 4/40 [p<0.05], and 9/41 [p<0.01]), a rare tumor in mice, was considered treatment-related by U.S. EPA (2005a).

In female mice, the incidences of hepatocellular adenoma (5/70, 3/70, 4/70, 27/70 [p<0.01] and 29/70 [p<0.01]) and combined hepatocellular adenoma or carcinoma (8/70, 4/70, 6/70, 29/70 [p<0.01] and 32/70 [p<0.01]) were significantly increased at the two highest dose levels and occurred with positive trends [p<0.01]. The incidence of hepatocellular carcinoma (3/70, 3/70, 3/70, 7/70, and 6/70) was also increased.

Mepanipyrim (CAS No. 110235-47-7)

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

The U.S. EPA (2004) has concluded that mepanipyrim is "Likely to be carcinogenic to humans" based on increased incidences of malignant, benign, and combined malignant and benign liver tumors in male and female mice and increased incidences of benign liver tumors in female rats. Studies evaluated by U.S. EPA (2004) are summarized below.

Male and female $B6C3F_1$ mice (50 animals/group/sex) were exposed to 0, 70, 350, 3500 or 7000 ppm mepanipyrim via diet for 104 weeks. In male mice, the incidences of hepatocellular adenoma (20/50, 11/50, 15/50, 30/50 [p<0.05] and 39/50 [p<0.01] for control, 70, 350, 3500 and 7000 ppm dose groups, respectively), hepatocellular carcinoma (12/50, 18/50, 14/50, 23/50 [p<0.05] and 23/50 [p<0.05]), and combined hepatocellular adenoma or carcinoma (26/50, 26/50, 25/50, 37/50 [p<0.05] and 44/50 [p<0.01]) were significantly increased in the two highest dose groups and occurred with positive trends [p<0.01]. Tumor incidences exceeded the historical control incidences in the testing laboratory which averaged 47% (range, 22-76%) for hepatocellular adenoma and 20.4% (range, 12-28%) for hepatocellular carcinoma. In female mice, the incidences of hepatocellular adenoma (8/50, 6/50, 10/50, 32/50 [p<0.01] and 38/49 [p<0.01]), hepatocellular carcinoma (3/50, 2/50, 3/50, 14/50 [p<0.01] and 30/49 [p<0.01]) and combined hepatocellular adenoma or carcinoma (11/50, 8/50, 13/50, 36/50 [p<0.01] and 44/49 [p<0.01]) were also significantly increased in the two highest dose groups and also occurred with positive trends [p<0.01]. The incidences exceeded the historical control incidences from the testing laboratory for both hepatocellular adenoma (mean, 14.6%; range, 8-32%) and hepatocellular carcinoma (mean, 6.4%, range, 2-12%).

Male and female Fischer 344 rats (50 animals/group/sex) were exposed to 0, 50, 150, 2000, or 4000 ppm mepanipyrim via diet for 104 weeks. In female rats, the incidence of hepatocellular adenoma (1/50, 1/49, 1/50, 4/50 and 13/50 [p<0.01] for control, 50, 150, 2000 and 4000 ppm dose groups, respectively) was significantly increased in the high-dose group. Two liver cystadenomas were also found in the high-dose group. The combined incidence of hepatocellular adenoma or cystadenoma was 1/50, 1/49, 1/50, 4/50 and 15/50 [p<0.01]. No treatment-related tumors were observed in male rats.

Pirimicarb (CAS No.23103-98-2)

Increased incidence of malignant and combined malignant and benign tumors in male and female mice, with tumors at multiple sites in female mice.

The U.S. EPA (2005b) has concluded that pirimicarb is "Likely to be carcinogenic to humans." This classification was based on malignant and benign tumors in male (liver, lung) and female (liver, lung, mammary gland, ovary) mice of one strain and on benign lung tumors in a second strain of female mice. The studies evaluated by U.S. EPA (2005b) are summarized below.

Male and female Swiss mice (60 animals/group/sex) were exposed to pirimicarb via diet for 94 weeks. In male mice, statistically significant increases in the incidences of hepatocellular adenoma (14/104, 5/51, 11/48 and 19/52 [p<0.01] for control, low-, mid-, and high-dose groups, respectively), hepatocellular carcinoma (10/104, 13/51 [p<0.05], 8/48, and 17/52 [p<0.01]), and combined hepatocellular adenoma or carcinoma (22/104, 18/51 [p<0.05], 17/48 [p<0.05] and 32/52 [p<0.01]) occurred with positive trends [p<0.01]. In addition, the incidence of lung adenoma (17/103, 9/51, 8/48 and 19/54 [p<0.01]; positive trend, p<0.01) was significantly increased in high-dose male mice.

In female mice, statistically significant increases in the incidences of hepatocellular carcinoma (2/95, 3/47, 3/47 and 5/32 [p<0.01] for control, low-, mid-, and high-dose groups, respectively) and combined hepatocellular adenoma or carcinoma (5/107, 6/53 [p<0.05], 9/53 [p<0.05] and 9/42 [p<0.01]) also occurred with positive trends [p<0.01]. The incidence of lung adenoma (13/108, 9/57, 11/56, and 18/52 [p<0.01]) was significantly increased in high-dose females (positive trend, p<0.01). Statistically significant increases in the incidences of mammary gland adenocarcinoma (0/94, 1/46, 0/48 and 4/30 [p<0.01]), combined mammary gland adenoma or adenocarcinoma (0/94, 1/46, 2/48, and 4/30 [p<0.01]), and ovarian papillary cystadenoma (0/75, 1/35, 3/44 and 3/24 [p<0.01]) all occurred with positive trends [p<0.01].

Male and female CD-1 mice (55 animals/group/sex) were exposed to pirimicarb via diet for 80 weeks. In female mice a statistically significant increase in lung adenomas (0/53, 0/52, 0/51 and 6/51 [p<0.01]) was observed.

Male and female Wistar rats (52 animals/group/sex) were exposed to pirimicarb via diet for 24 months. No treatment-related tumors were found in either male or female rats.

Resmethrin (CAS No. 10453-86-8)

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

U.S. EPA (2005c) has concluded that resmethrin is "Likely to be carcinogenic to humans" based on an increased incidence of malignant and combined malignant and benign liver tumors in female rats and male mice. The studies evaluated by U.S. EPA (2005c) are summarized below.

Male and female Sprague-Dawley rats (65 animals/group/sex) were exposed to resmethrin via diet for 24 months. In female rats, increases in the incidences of hepatocellular adenoma (0/56, 0/52, 1/54, and 3/54 [$p<0.05$] for control, low-, mid- and high-dose groups, respectively), hepatocellular carcinoma (1/51, 0/45, 0/48 and 11/45 [$p<0.01$]), and combined hepatocellular adenoma or carcinoma (1/56, 0/52, 1/54, and 14/54 [$p<0.01$]) were statistically significant and occurred with positive trends [$p<0.01$]. No treatment-related tumors were observed in male rats.

Male and female CD-1 mice (50 animals/group/sex) were exposed to resmethrin via diet for 24 months. In male mice, increased incidences of hepatocellular adenoma (9/96, 9/45 [$p<0.05$], 12/47 [$p<0.01$], and 15/47 [$p<0.01$] for control, low-, mid- and high-dose groups, respectively); hepatocellular carcinoma (2/85, 2/39, 4/35 [$p<0.05$], and 6/37 [$p<0.01$]); and combined hepatocellular adenoma or carcinoma (11/96, 10/45 [$p<0.05$], 14/47 [$p<0.01$] and 18/47 [$p<0.01$]) were statistically significantly greater than that in control animals and occurred with positive trends [$p<0.01$]. No treatment-related tumors were observed in female mice.

References

U.S. Environmental Protection Agency (U.S. EPA, 2004). *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Mepanipyrim.* Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. April 20, 2004.

U.S. Environmental Protection Agency (U.S. EPA, 2005a). *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Benthiavalicarb-isopropyl.* Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs. October 18, 2005.

U.S. Environmental Protection Agency (U.S. EPA, 2005b). *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Pirimicarb.* Cancer Assessment Review Committee. Health Effects Division. Office of Pesticide Programs. July 13, 2005.

U.S. Environmental Protection Agency (U.S. EPA, 2005c). *Cancer Assessment Document. Evaluation of the Carcinogenic Potential of Resmethrin.* Cancer Assessment Review Committee, Health Effects Division, Office of Pesticide Programs. May 25, 2005.