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 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 National Toxicology Program (NTP) 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]). NTP has identified the chemicals in the table below as causing cancer. The Office of Environmental Health Hazard Assessment (OEHHA) has found that these chemicals appear to be "formally identified" as causing cancer according to the regulations covering this issue (Section 12306[d]). The chemicals below are the subjects of reports published by NTP 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 given in regulation for "as causing cancer" (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 NTP 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 (Section 12306[e]). The full citations for the 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

Chemical	CAS No.	Chemical Use	Reference
Dibromoacetic Acid	631-64-1	Water disinfection by-product.	NTP (2007a)
4-Methylimidazole	822-36-6	Used in the manufacture of pharmaceuticals, photographic chemicals, dyes and pigments, cleaning and agricultural chemicals, and rubber. Fermentation by-product in cattle fed ammoniated forage and in certain food products including caramel coloring, soy sauce, Worcestershire sauce, wine, and ammoniated molasses.	NTP (2007b)

Dibromoacetic acid (CAS No. 631-64-1)

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

The NTP (2007a) has concluded that there is clear evidence of the carcinogenic activity of dibromoacetic acid in male and female $B6C3F_1$ mice.

The NTP (2007a) exposed male and female F344/N rats and $B6C3F_1$ mice (50 animals/group/sex) to dibromoacetic acid in drinking water for two years. In male mice, statistically significant increases in the incidences of hepatocellular adenoma (18/49, 37/50 [$p<0.001$], 37/50 [$p<0.001$] and 42/50 [$p<0.001$] for control, low-, mid- and high-dose groups, respectively), hepatocellular carcinoma (14/49, 9/50, 19/50 and 26/50 [$p<0.05$]) and combined hepatocellular adenoma or carcinoma (28/49, 41/50 [$p<0.01$], 42/50 [$p<0.001$] and 47/50 [$p<0.001$]) all occurred with positive trends [$p<0.001$]. The increased incidence of hepatoblastoma (0/49, 4/50, 6/50 [$p<0.05$] and 18/50 [$p<0.001$]) and the combined incidence of hepatocellular adenoma, carcinoma or hepatoblastoma (28/49, 41/50 [$p<0.01$], 43/50 [$p<0.001$], and 48/50 [$p<0.001$]) also occurred with positive trends [$p<0.001$]. In addition, incidences of alveolar/bronchiolar adenoma (7/49, 5/50, 17/50 [$p<0.05$], and 12/50) and alveolar/bronchiolar adenoma or carcinoma (12/49, 12/50, 22/50 [$p<0.05$], and 17/50) were significantly increased in mid-dose male mice. NTP considered the increase in lung tumors in male mice to be related to dibromoacetic acid exposure.

In female mice, statistically significant increases in the incidences of hepatocellular adenoma (19/49, 26/50, 32/50 [$p<0.01$] and 35/49 [$p<0.001$]), hepatocellular carcinoma (3/49, 3/50, 12/50 [$p<0.01$], and 8/49) and combined hepatocellular adenoma or carcinoma (22/49, 28/50, 37/50 [$p<0.001$] and 37/49 [$p<0.001$]) occurred with positive trends ($p<0.001$, for hepatocellular adenoma and combined hepatocellular adenoma or carcinoma; $p<0.05$, for hepatocellular carcinoma). Female mice also had an increase in combined alveolar/bronchiolar adenoma or carcinoma (2/50, 5/50, 5/50, and 7/50), and

NTP concluded that the increase in lung tumors in female mice may have been related to dibromoacetic acid exposure.

NTP (2007a) concluded that there was some evidence of carcinogenicity in male rats based on an increased incidence of malignant mesothelioma (all organs) (3/50, 1/50, 0/50 and 10/50 [$p<0.05$]); NTP found that the increase in mononuclear cell leukemia (17/50, 31/50, 24/50 and 13/50) in male rats may have been related to dibromoacetic acid exposure. NTP (2007a) concluded that there was some evidence of carcinogenicity in female rats based on an increased incidence and positive trend of mononuclear cell leukemia (11/50, 13/50, 16/50 and 22/50 [$p<0.05$]).

NTP (2007a) tested dibromoacetic acid with *Salmonella typhimurium* strains TA98 and TA100. Dibromoacetic acid was mutagenic in strain TA100 with or without liver metabolic activation enzymes. No activity was found in strain TA98 with or without liver metabolic activation enzymes. Dibromoacetic acid tested negative in a mouse peripheral blood micronucleus test.

4-Methylimidazole (CAS No. 822-36-6)

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

The NTP (2007b) has concluded that there is clear evidence of the carcinogenic activity of 4-methylimidazole in male and female $B6C3F_1$ mice.

NTP (2007b) exposed male and female F344/N rats and $B6C3F_1$ mice (50 animals/group/sex) to 4-methylimidazole via diet for two years. In male mice, the incidence of alveolar/bronchiolar carcinoma (2/50, 4/50, 4/50 and 8/50 [$p<0.05$] for control, low-, mid-, and high-dose groups, respectively) was significantly increased and occurred with a positive trend [$p<0.05$]. The combined incidence of alveolar/bronchiolar adenoma or carcinoma (9/50, 13/50, 16/50, and 22/50 [$p<0.01$]) also occurred with a positive trend [$p<0.001$]. Tumor incidences exceeded the NTP historical control incidence in male $B6C3F_1$ mice for alveolar/bronchiolar carcinoma (mean, 7.8%; range, 4-14%) and combined alveolar/bronchiolar adenoma or carcinoma (mean, 22.2%; range, 14-32%).

In female mice, the incidences of alveolar/bronchiolar adenoma (0/50, 8/50 [$p<0.01$], 16/50 [$p<0.001$] and 8/50 [$p<0.01$]) and combined alveolar/bronchiolar adenoma or carcinoma (3/50, 8/50, 17/50 [$p<0.001$], and 14/50 [$p<0.01$]) were significantly greater than that in control animals and occurred with positive trends ($p<0.05$, for alveolar/bronchiolar adenoma and $p<0.01$, for combined alveolar/bronchiolar adenoma or carcinoma. The tumor incidence exceeded the NTP historical control incidence for combined alveolar/bronchiolar carcinoma or adenoma (mean, 6.6%; range, 0-12%).

NTP (2007b) concluded that there was equivocal evidence of carcinogenicity in female rats, based on an increase in mononuclear cell leukemia. NTP (2007b) found no evidence of carcinogenicity in male rats.

References

National Toxicology Program (NTP, 2007a). *Toxicology and Carcinogenesis Studies of Dibromoacetic Acid (CAS No. 631-64-1) in F344/N Rats and B6C3F$_1$ Mice (Drinking Water Studies).* NTP Technical Report Series No. 537. NIH Publication No. 07-4475. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

National Toxicology Program (NTP, 2007b). *Toxicology and Carcinogenesis Studies of 4-Methylimidazole (CAS No. 822-36-6) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies).* NTP Technical Report Series No. 535. NIH Publication No. 07-4471. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.