

**CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT**

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

**NOTICE OF INTENT TO LIST: ANDROSTENEDIONE, DIBROMOACETONITRILE,
HEXACHLOROBUTADIENE, AND MALONALDEHYDE, SODIUM SALT**

March 4, 2011

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) intends to list the chemicals *androstenedione*, *dibromoacetonitrile*, *hexachlorobutadiene*, and *malonaldehyde, sodium salt* as known to the State to cause cancer under the Safe Drinking Water and Toxic Enforcement Act of 1986.¹ This action is being proposed under the authoritative bodies listing mechanism.²

Chemical (CAS No.)	Endpoint	Reference	Occurrence
<i>Androstenedione</i> (63-05-8)	Cancer	NTP (2010a)	Precursor to male and female sex hormones produced by the human body; dietary supplement currently designated as a controlled substance under federal law ^a
<i>Dibromoacetonitrile</i> (3252-43-5)	Cancer	NTP (2010b)	By-product of drinking water disinfection by ozone or chlorination disinfection processes in the presence of natural organic matter and bromine
<i>Hexachlorobutadiene</i> (87-68-3)	Cancer	U.S. EPA (2003)	Waste by-product from hydrocarbon chlorination processes; chemical intermediate in the manufacture of rubber, chlorofluorocarbons, lubricants, and transformer and hydraulic fluids
<i>Malonaldehyde, sodium salt</i> (24382-04-5)	Cancer	NTP (1988)	The sodium salt of malonaldehyde is unlikely to occur in nature, and has no industrial use. Malonaldehyde is a natural metabolic by-product of prostaglandin biosynthesis and an end product of polyunsaturated lipid peroxidation.

^a Title 21 U.S. Code, Sec. 802(41)(A).

OEHHA requested information relevant to the possible listing of *androstenedione*, *dibromoacetonitrile*, *hexachlorobutadiene*, and *malonaldehyde, sodium salt* in a notice

¹ Commonly known as Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986 is codified in Health and Safety Code section 25249.5 *et seq.*

² See Health and Safety Code section 25249.8(b) and Title 27, Cal. Code of Regs., section 25306.

published in the *California Regulatory Notice Register* on November 26, 2010 (Register 2010, Vol. No. 48-Z). OEHHA received no public comments.

Background on listing via the authoritative bodies mechanism: A chemical must be listed under the Proposition 65 regulations when two conditions are met:

- 1) An authoritative body formally identifies the chemical as causing cancer (Section 25306(d)³).
- 2) The evidence considered by the authoritative body meets the sufficiency criteria contained in the regulations (Section 25306(e)).

However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306(f)).

The National Toxicology Program (NTP) and the U.S. Environmental Protection Agency (U.S. EPA) are two of several institutions designated as authoritative for the identification of chemicals as causing cancer (Section 25306(m)).

OEHHA is the lead agency for Proposition 65 implementation. After an authoritative body has made a determination about a chemical, OEHHA evaluates whether listing under Proposition 65 is required using the criteria contained in the regulations.

OEHHA's determination: *Androstenedione, dibromoacetonitrile, hexachlorobutadiene, and malonaldehyde, sodium salt* each meet the criteria for listing as known to the State to cause cancer under Proposition 65, based on findings of the NTP and the U.S. EPA.

Formal identification and sufficiency of evidence for androstenedione: In 2010, the NTP published a report on androstenedione, entitled *Toxicology and Carcinogenesis Studies of Androstenedione (CAS No. 63-05-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*, that concludes that the chemical causes cancer (NTP, 2010a). This report satisfies the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the NTP's discussion of data and conclusions in the report that androstenedione causes cancer. The NTP (2010a) report concludes:

"Under the conditions of these 2-year gavage studies, there was equivocal evidence of carcinogenic activity of androstenedione in male F344/N rats based on increased incidences of alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined). There was equivocal evidence of carcinogenic activity of androstenedione in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was clear evidence of carcinogenic activity of androstenedione in male B6C3F1 mice based on increased incidences of multiple hepatocellular adenoma and hepatocellular carcinoma and increased incidence of hepatoblastoma. There was clear evidence of carcinogenic

³ All referenced sections are from Title 27 of the Cal. Code of Regulations.

activity of androstenedione in female B6C3F1 mice based on increased incidences of hepatocellular adenoma and hepatocellular carcinoma. Increased incidences of pancreatic islet adenoma in male and female mice were also considered chemical related.” (Emphasis in original)

Thus, the NTP (2010a) has found that androstenedione causes increased incidences of malignant and combined malignant and benign liver tumors in male and female mice.

Formal identification and sufficiency of evidence for dibromoacetonitrile: In 2010, the NTP published a report on dibromoacetonitrile, entitled *Toxicology and Carcinogenesis Studies of Dibromoacetonitrile (CAS No. 3252-43-5) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies)*, that concludes that the chemical causes cancer (NTP, 2010b). This report satisfies the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the NTP’s discussion of data and conclusions in the report that dibromoacetonitrile causes cancer. The NTP (2010b) report concludes:

“Under the conditions of these 2-year drinking water studies there was *clear evidence of carcinogenic activity* of dibromoacetonitrile in male rats based on increased incidences of squamous cell papillomas or carcinomas of the oral cavity; adenomas in the glandular stomach of male rats were also considered to be exposure-related. There was *some evidence of carcinogenic activity* of dibromoacetonitrile in female rats based on an increased incidence of squamous cell papillomas of the oral cavity; increased incidences of basal cell or squamous cell neoplasms of the skin in female rats may have been related to dibromoacetonitrile exposure. There was *clear evidence of carcinogenic activity* of dibromoacetonitrile in male mice based on increased incidences of squamous cell papillomas or carcinomas of the forestomach. Increased incidences of neoplasms in the liver of male mice may have been related to dibromoacetonitrile exposure. There was *clear evidence of carcinogenic activity* of dibromoacetonitrile in female mice based on increased incidences of squamous cell papilloma of the forestomach.”
(Emphasis in original)

Thus, the NTP (2010b) has found that dibromoacetonitrile causes increased incidences of combined malignant and benign tumors of the oral cavity in male rats and combined malignant and benign forestomach tumors in male mice.

Formal identification and sufficiency of evidence for hexachlorobutadiene: In 2003, the U.S. EPA published a report on hexachlorobutadiene, entitled *Health Effects Support Document for Hexachlorobutadiene*, that concludes that the chemical causes cancer (U.S. EPA, 2003). This report satisfies the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the U.S. EPA's discussion of data and conclusions in the report that hexachlorobutadiene causes cancer. The U.S. EPA (2003) report concludes that hexachlorobutadiene is "likely to be carcinogenic to humans by the oral route of exposure." In its report, the U.S. EPA describes studies of rats treated with hexachlorobutadiene in their diet for two years showing increases in the incidence of malignant tumors (e.g., adenocarcinomas) of the renal tubule in male and female rats and incidences of combined malignant and benign tumors of the renal tubules in both male and female rats.

Thus, the U.S. EPA (2003) has found that hexachlorobutadiene causes increased incidences of malignant and combined malignant and benign kidney tumors in male and female rats.

Formal identification and sufficiency of evidence for malonaldehyde, sodium salt: In 1988, the NTP published a report on malonaldehyde, sodium salt, entitled *Toxicology and Carcinogenesis Studies of Malonaldehyde, Sodium Salt (3-Hydroxy-2-propenal, Sodium Salt) (CAS No. 24382-04-5) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*, that concludes that the chemical causes cancer (NTP, 1988). This report satisfies the formal identification and sufficiency of evidence criteria in the Proposition 65 regulations.

OEHHA is relying on the NTP's discussion of data and conclusions in the report that malonaldehyde, sodium salt causes cancer. The NTP (1988) report concludes:

"Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity* for male and female F344/N rats administered malonaldehyde, sodium salt, as shown by the increased incidences of follicular cell adenomas or carcinomas (combined) of the thyroid gland. Pancreatic islet cell adenomas were also observed at an increased incidence in low dose male rats. There was *no evidence of carcinogenic activity* for B6C3F₁ mice administered 60 or 120 mg/kg malonaldehyde, sodium salt, in distilled water by gavage 5 days per week for 2 years." (Emphasis in original)

Thus, NTP (1988) has found that malonaldehyde, sodium salt causes increased incidences of combined malignant and benign tumors of the thyroid gland in male and female rats.

Request for comments: OEHHA is committed to public participation in its implementation of Proposition 65. OEHHA wants to ensure that its regulatory decisions are based on a thorough consideration of all relevant information. OEHHA is requesting comments as to whether these chemicals meet the criteria set forth in the Proposition 65 regulations for authoritative bodies listings. In order to be considered, **OEHHA must receive comments by 5:00 p.m. on Monday, April 4, 2011.** We encourage you to submit comments in electronic form, rather than in paper form. Comments transmitted by e-mail should be addressed to coshita@oehha.ca.gov.

Comments submitted in paper form may be mailed, faxed, or delivered in person to the addresses below:

Mailing Address: Ms. Cynthia Oshita
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P.O. Box 4010, MS-19B
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Sacramento, California 95814

If you have any questions, please contact Ms. Oshita at coshita@oehha.ca.gov or at (916) 445-6900.

References

National Toxicology Program (NTP, 1988). *Toxicology and Carcinogenesis Studies of Malonaldehyde, Sodium Salt (3-Hydroxy-2-propenal, Sodium Salt) (CAS No. 24382-04-5) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*. NTP Technical Report Series No. 331. NIH Publication No. 89-2587, U.S. Department of Health and Human Services, NTP Research Triangle Park, NC.

National Toxicology Program (NTP, 2010a). *Toxicology and Carcinogenesis Studies of Androstenedione (CAS No. 63-05-8) in F344/N Rats and B6C3F1 Mice (Gavage Studies)*. NTP Technical Report Series No. 560. NIH Publication No. 10-5901. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

National Toxicology Program (NTP, 2010b). *Toxicology and Carcinogenesis Studies of Dibromoacetonitrile (CAS No. 3252-43-5) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies)*. NTP Technical Report Series No. 544. NIH Publication No. 10-5886. U.S. Department of Health and Human Services, NTP, Research Triangle Park, NC.

U.S. Environmental Protection Agency (U.S. EPA, 2003). *Health Effects Support Document for Hexachlorobutadiene*. Health and Ecological Criteria Division, Office of Water. EPA 822-R-03-002, February 2003.