

**CHEMICAL MEETING THE CRITERIA FOR LISTING AS CAUSING
CANCER VIA THE AUTHORITATIVE BODIES MECHANISM:
4-METHYLIMIDAZOLE**

PACKAGE 32b

March 2009

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

4-Methylimidazole meets 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 25306¹. 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[1]). NTP has identified 4-methylimidazole as causing cancer. OEHHA has found that this chemical is “formally identified” as causing cancer according to the regulations covering this issue (Section 25306[d]). 4-Methylimidazole is the subject of a report published by NTP that concludes that the chemical causes cancer. Also, the document specifically and accurately identifies the chemical, and the document meets one or more of the criteria outlined in Section 25306(d)(2).

OEHHA also finds that the criteria given in regulation for “as causing cancer” (Section 25306[e]) have been satisfied for 4-methylimidazole. In making this evaluation, OEHHA relied upon the discussion of data by the NTP in making its finding that 4-methylimidazole causes cancer. A brief discussion of the relevant carcinogenesis studies providing evidence for the finding is presented below. The statement in bold reflects data and conclusions that satisfy the criteria for the sufficiency of evidence for carcinogenicity (Section 25306[e]). The full citation for the document is given in this report.

¹ Formally Title 22, California Code of Regulations, section 12306. All further references are to Title 27 of the California Code of Regulations unless otherwise indicated.

Chemical Meeting the Criteria for Listing as Known to the State to Cause Cancer

Chemical	CAS No.	Chemical Use	Reference
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 (2007)

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 (2007) has concluded that there is clear evidence of the carcinogenic activity of 4-methylimidazole in male and female B6C3F₁ mice.

NTP (2007) exposed male and female F344/N rats and B6C3F₁ 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 B6C3F₁ 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 (2007) concluded that there was equivocal evidence of carcinogenicity in female rats, based on an increase in mononuclear cell leukemia. NTP (2007) found no evidence of carcinogenicity in male rats.

References

National Toxicology Program (NTP, 2007). *Toxicology and Carcinogenesis Studies of 4-Methylimidazole (CAS No. 822-36-6) in F344/N Rats and B6C3F₁ 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.