

**CHEMICAL UNDER CONSIDERATION FOR POSSIBLE LISTING  
VIA THE AUTHORITATIVE BODIES MECHANISM**

**PACKAGE 23**

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

The chemical listed in the table below may meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism as known to the State to cause cancer. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations, section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

The National Toxicology Program (NTP) is one of five institutions which have been identified as authoritative bodies for identification of chemicals as causing cancer for the purposes of Proposition 65 (Title 22, Cal. Code of Regs., section 12306(1)). The NTP has identified the chemical below as causing cancer. The Office of Environmental Health Hazard Assessment (OEHHA) has found that the chemical appears to be “formally identified” as causing cancer according to the regulations covering this issue (Title 22, Cal. Code of Regs., section 12306[d]). The chemical 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 Title 22, Cal. Code of Regs., section 12306(d)(2).

OEHHA also finds that the criteria given in regulation for “as causing cancer” (Title 22, Cal. Code of Regs., section 12306[e]) appear to have been satisfied for the chemical in the table below. In making this evaluation, OEHHA relied upon the discussion of data by the authoritative body in making its finding that the chemical 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 appear to satisfy the criteria for the sufficiency of evidence for carcinogenicity (Title 22, Cal. Code of Regs., section 12306[e]). The full citation for the authoritative body document is given in this report.

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

| <b>Chemical</b>                                                       | <b>CAS No.</b> | <b>Chemical Use</b>                                                                                                                                                   | <b>Reference</b> |
|-----------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 2,4-Hexadienal<br>(89% trans, trans isomer;<br>11% cis, trans isomer) | -----          | Food additive used for flavoring and fragrance; starting material or intermediate in chemical and pharmaceutical industries, fumigant, corrosion inhibitor for steel. | NTP (2003)       |

2,4-Hexadienal (89% trans, trans isomer; 11% cis, trans isomer)

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

NTP (2003) has concluded that there is clear evidence of the carcinogenic activity of 2,4-hexadienal (89% trans, trans isomer, CAS No. 142-83-6; 11% cis, trans isomer) in both sexes of B6C3F<sub>1</sub> mice and F344/N rats.

NTP (2003) treated male and female B6C3F<sub>1</sub> mice and F344/N rats (50 animals/group/sex) with 2,4-hexadienal (89% trans, trans isomer; 11% cis, trans isomer) in corn oil by gavage five days per week for two years. Forestomach tumors were observed in both mice and rats exposed to 2,4-hexadienal.

In male rats, exposure to 2,4-hexadienal resulted in a statistically significant increase in combined malignant and benign squamous cell tumors of the forestomach. The incidence of combined forestomach squamous cell papilloma or carcinoma was 0/50, 3/50 (p=0.1), 11/50 (p < 0.001), and 29/50 (p < 0.001) for control, low-, mid- and high-dose animals, respectively. Squamous cell papilloma of the forestomach was significantly elevated (0/50, 3/50, 10/50 [p<0.001], and 29/50 [p<0.001]). Multiple papillomas were common in male rats in the high-dose group. Forestomach tumors are uncommon in F344/N rats. The incidence of forestomach papillomas in all 2,4-hexadienal treatment groups exceeded the overall incidence in historical control animals. In control male rats (all routes of exposure) given the NTP-2000 diet, the historical control incidence of this tumor was 2/609, with the observed papillomas occurring in two separate studies (1/50, 1/100). In corn oil vehicle control animals given the NIH-07 diet, the historical control incidence was 2/402, with a range of 0-2%. Following exposure to 2,4-hexadienal, squamous cell carcinomas of the forestomach were observed in one mid-dose male rat and two high-dose male rats (p≤0.01 compared to historical controls). The current NTP historical control database indicates no squamous cell carcinomas of the forestomach were found in

609 male rats fed the NTP-2000 diet (all routes) or in 402 corn oil gavage controls given the NIH-07 diet.

In female F344/N rats, the incidence of squamous cell papilloma [0/50, 1/50, 5/50, 17/50] was significantly greater in mid- and high-dose animals compared to control animals ( $p=0.031$  and  $p<0.001$ , respectively). No forestomach carcinomas were observed in female rats.

NTP (2003) treated male and female B6C3F<sub>1</sub> mice (50 animals/group/sex) with 2,4-hexadienal in corn oil by gavage five days per week for two years. In male mice, the combined incidence of forestomach squamous cell papilloma or carcinoma (2/50, 4/50, 5/50, 10/50 for control, low-, mid- and high-dose groups, respectively) was significantly greater in high-dose male mice compared to that in control animals ( $p=0.009$ ). The incidence of squamous cell papilloma of the forestomach was 2/50, 4/50, 5/50, and 8/50. Squamous cell carcinomas were observed in one low-dose and two high-dose mice. NTP (2003) also reported two squamous cell carcinomas of the oral cavity (tongue) in male mice treated with the high-dose of 2,4-hexadienal. This incidence exceeded historical incidences in controls (all routes) given the NTP-2000 diet [0/659] or corn oil gavage controls given the NIH-07 diet [0/464]. NTP (2003) concluded that the development of this uncommon neoplasm (squamous cell carcinoma of the oral cavity) may have been related to 2,4-hexadienal administration.

In female mice, the combined incidence of forestomach squamous cell papilloma or carcinoma (2/50, 2/49, 11/50, 18/50) was significantly greater in the mid- and high-dose groups compared to the incidence in control animals ( $p=0.006$  and  $p<0.001$ , respectively). The incidence of forestomach squamous cell papilloma was 2/50, 2/49, 2/11, and 13/50. Forestomach squamous cell carcinomas were observed in seven female mice in the high-dose group. The historical incidence for this tumor in the NTP-2000 diet is 1/659 and for the NIH-07 diet, 0/463. In three of the seven females with forestomach carcinoma, metastases occurred to various organs (mesentery, pancreas, esophagus, ovary and lymph nodes).

NTP (2003) also found that 2,4-hexadienal was mutagenic in *Salmonella typhimurium* strain TA100 with and without metabolic liver enzymes. Mutagenicity was not detected with strains TA1535 or TA98. Although bone marrow tests in male rats and male mice given 2,4-hexadienal intraperitoneally showed a small increase in the induction of micronucleated erythrocytes, these results were judged to be inconclusive. Results of peripheral blood micronucleus tests in male and female mice were negative.

**REFERENCE**

National Toxicology Program (NTP, 2003). *Toxicology and Carcinogenesis Studies of 2,4-Hexadienal (89% trans, trans isomer, CAS No. 142-83-6; 11% cis, trans isomer) in F344/N Rats and B6C3F<sub>1</sub> Mice (Gavage Studies)*. NTP Technical Report Series No. 509. NIH Publication No. 04-4443. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, NTP, Research Triangle Park, NC.