

PHENOLPHTHALEIN UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

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

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The chemical listed in the following table, phenolphthalein, may meet the criteria for the listing of carcinogens formally identified by an authoritative body, as set forth in Title 22, California Code of Regulations, Section 12306. Information on the occurrence and usage of this chemical and the relevant references to the authoritative body publications are also given. A summary of the results of relevant studies of the chemical follows the table.

Chemical Under Consideration for Possible Listing as a Carcinogen

Chemical	CAS No.	Identity of chemical	Reference
Phenolphthalein	77-09-8	Cathartic drug in laxatives; sold over-the counter. Laboratory reagent. Dyes.	NTP (1996) FDA, 1997

Summarized below are the relevant carcinogenesis studies and conclusions for phenolphthalein, a chemical under evaluation as potentially having satisfied the criteria for listing under the authoritative bodies provision of Proposition 65, as set forth in 22 CCR Section 12306. A document published by the National Toxicology Program (NTP), one of the five Proposition 65 authoritative bodies, was the primary source for the summary. The statement in bold reflects data and conclusions that appear to satisfy the criteria for the sufficiency of evidence for carcinogenicity in subsection (e) Section 12306. The evidence for the carcinogenicity of the chemical is only briefly discussed here. The full citations for the primary source documents are given in this report. The primary source documents, on file at OEHHA, provide additional details on the critical studies described below.

Phenolphthalein (CAS No. 77-09-8)

Positive cancer bioassays in two species, with multiple sites in mice.

The National Toxicology Program (NTP, 1996) has concluded that there is clear evidence of carcinogenic activity of phenolphthalein in male F344/N rats and in male and female B6C3F₁ mice.

NTP (1996) administered phenolphthalein to F344/N rats and B6C3F₁ mice via diet for two years. In male rats, NTP observed significantly increased incidences of benign

pheochromocytomas of the adrenal medulla in phenolphthalein-treated animals (17/50, 34/50, 34/50, and 34/50 for control, low-, mid- and high-dose groups, respectively). There were also markedly increased incidences of renal tubule adenomas (1/50, 10/50, 15/50, 15/50) and combined adenomas or carcinomas (1/50, 10/50, 16/50, 16/50) in treated males.

In mice, phenolphthalein treatment resulted in a statistically significant increase in the incidence of histiocytic sarcoma in mid- and high-dose males and females. The incidences were 1/50, 3/50, 11/50 and 12/49 in males, and 0/50, 2/50, 7/50 and 7/50 in females for control, low-, mid- and high-dose groups, respectively. Significant increases in lymphomas of thymic origin were observed in mid-dose males (0/50, 4/50, 7/50, 2/49) and in all dose-groups of female mice (1/50, 9/50, 10/50, 7/50). In female mice, there were also statistically significant increases in the incidence of malignant lymphoma of all types (15/50, 28/50, 33/50, 25/50) and benign sex-cord stromal tumors of the ovary (0/50, 7/49, 6/50, 5/50). NTP noted that ovarian neoplasms are uncommon in B6C3F₁ mice.

NTP concluded that there was some evidence of carcinogenic activity of phenolphthalein in female F344/N rats based on increased incidences of benign pheochromocytomas of the adrenal medulla in low-dose animals (3/50, 11/50, 9/50, 2/49) and of benign or malignant pheochromocytomas (combined) in low- and mid-dose animals (3/50, 12/50, 10/50, 2/49).

The Food and Drug Administration's Carcinogenicity Assessment Committee (CAC) met on April 30, 1997 to discuss the carcinogenic potential of phenolphthalein (FDA, 1997). Relevant information reviewed by the Committee included the NTP technical report on phenolphthalein (NTP, 1996) and findings from more recent studies in a p53 transgenic mouse model and in Syrian hamster embryo cells (NTP, unpublished data). The CAC concluded 15 to 1, with one abstention, that based on the totality of the data, the results indicate a relevant carcinogenic risk for humans under conditions of exposure encountered with use of phenolphthalein as an OTC (over-the-counter) laxative (FDA, 1997).

References

National Toxicology Program (NTP, 1996). Toxicology and Carcinogenesis Studies of Phenolphthalein (CAS No. 77-09-8) in F344/N Rats and B6C3F₁ Mice (Feed Studies). NTP Technical Report Series No. 465. NTIS Publication No. 97-3390. US Department of Health and Human Services, NTP, Research Triangle Park, NC.

Food and Drug Administration (FDA, 1997). Minutes from the Carcinogenicity Assessment Committee (CAC) Meeting, April 30, 1997, US Department of Health and Human Services, Public Health Service, Food and Drug Administration.