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 under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), 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) and the International Agency for Research on Cancer (IARC) are two of five institutions which have been identified as authoritative bodies for the purposes of Proposition 65 (22 CCR 12306(l)). One of these bodies has identified each of the chemicals in the table below as causing cancer. OEHHA has found that these chemicals appear to be "formally identified" as causing cancer according to the regulations covering this issue (22 CCR 12306(d)). The chemicals below are the subject of reports published by the authoritative bodies which 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 22 CCR 12306(d)(2).

OEHHA also finds that the criteria given in regulation for "as causing cancer" (22 CCR 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 authoritative bodies 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 (22 CCR 12306(e)). The full citations for the authoritative body documents are given in this report.

Chemicals Under Consideration for Possible Listing as Carcinogens

Chemical	CAS No.	Chemical Use	Reference
Diethanolamine	111-42-2	Preparation of soaps, cosmetics, shampoos and hair conditioners; solvent for intravenous drug administration; anticorrosion agent; also in textile processing and preparation of agricultural chemicals.	NTP (1997a) NTP (1997b)
Palygorskite fibers (> 5μm in length)	12174-11-7	Pet waste absorbent; oil and grease absorbent; drilling mud; also in fertilizers and pesticides.	IARC (1997)
Pyridine	110-86-1	Industrial and laboratory solvent; denaturant in alcohol and antifreeze mixtures; intermediate in insecticide, herbicide, and fungicide manufacture; intermediate and solvent in preparation of vitamins, drugs, dyes, textile water repellents and flavoring agents in food.	NTP (1997c) NTP (1997b)

Diethanolamine (CAS No. 111-42-2)

Increased incidence of malignant tumors in male and female mice and in multiple studies to an unusual degree with regard to high incidence in female mice.

NTP (1997a; 1997b) has concluded that there is clear evidence of carcinogenic activity of diethanolamine in male and female B6C3F_1 mice.

NTP (1997a) treated male and female F344/N rats and B6C3F_1 mice with diethanolamine dermally for two years. In mice diethanolamine exposure (40, 80, or 160 mg/kg) resulted in statistically significant increases in hepatocellular neoplasms. Diethanolamine exposure resulted in statistically significant increases in hepatocellular carcinoma in females at all doses (5/50, 19/50, 38/50, 42/50) and in males at the two highest doses (12/50, 17/50, 33/50, 34/50). High incidences of hepatocellular adenoma were also observed in animals of both sexes. In male mice, there was a statistically significant increase in the incidence of uncommon hepatoblastoma in mid- and high-dose animals (0/50, 2/50, 8/50, 5/50).
The average size and multiplicity of liver neoplasms was also considerably greater in diethanolamine-treated animals than in vehicle controls. NTP (1997a) noted that a diagnosis of multiple adenomas in vehicle control mice often corresponded to two neoplasms, whereas in diethanolamine-exposed mice (especially high-dose mice), multiple adenomas corresponded to five or more separate neoplasms.

In male mice, the incidence of renal tubule adenoma occurred with a significant positive trend. For standard (single sections) and extended (step sections) evaluations combined, the incidence was 1/50, 6/50, 8/50 and 7/50 for control, low-, mid- and high-dose groups, respectively).

No evidence of a carcinogenic response was observed in male or female rats. However, in 13-week prechronic studies, diethanolamine caused a strong toxic response in rats. In the 2-year study, doses were lowered to avoid the excessive dermal toxicity which was reported in the 13-week studies. Thus, doses administered to the rat in the 2-year study (16, 32, and 64 mg/kg for low-, mid- and high-dose groups, respectively) were far lower than those used in the mouse study. Percutaneous absorption of diethanolamine is reported to be more rapid through mouse skin than through rat skin. Because the rate of diethanolamine elimination is very similar in rats and mice, NTP concluded that the systemic exposure experienced by rats during the 2-year study was considerably less than that by mice.

NTP also conducted a series of separate studies on three commonly used diethanolamine condensates: coconut oil diethanolamine, lauric acid diethanolamine and oleic acid diethanolamine. Varying amounts of unreacted diethanolamine were present in each of the condensates, exposing the animals in these studies to a wide range of diethanolamine concentrations. The incidence of hepatocellular neoplasms in exposed male and female mice was associated with the concentration of free diethanolamine in the condensate in these studies (NTP, 1997a). As in the case for diethanolamine, the incidence of hepatocellular neoplasms was greater in female mice than in males. The greatest concentration of free diethanolamine was found in coconut oil acid diethanolamine condensate. In that study, $B6C3F_1$ mice were exposed to 0, 19.6 or 39.2 mg/kg free diethanolamine and increases in hepatocellular tumors were observed in both male and female mice. The incidence of hepatocellular carcinoma in female mice was 3/50, 21/50, 32/50 for control, low- and high-dose groups, respectively. In animals treated with lauric acid diethanolamine condensate, statistically significant increases in liver tumors were observed in female mice only. Animals treated with oleic acid diethanolamine were exposed to very low amounts of unreacted diethanolamine, and no carcinogenic response was observed (as summarized in NTP, 1997a).

The biological action of diethanolamine is based on its incorporation into phospholipids in place of ethanolamine. NTP (1997a) states that "the pathways of phospholipid biosynthesis using ethanolamine and choline are highly conserved and essentially the same in all mammals, as is the function of phospholipids as structural components of cell membranes and their role as second messengers. Therefore, it is likely that incorporation of diethanolamine into phospholipids would occur in any suitably exposed mammalian species." The report concludes that "...the carcinogenic responses that occurred in the 2-year study in mice represent potential hazards to humans exposed to diethanolamine."

These findings were published in a draft technical report and were subsequently reviewed and accepted at the December 9-10, 1997 NTP Technical Review Subcommittee Meeting as reported in the *Summary Minutes* for that meeting (NTP, 1997b).

Palygorskite fibers (>5μm in length) (CAS No. 12174-11-7)

Increased incidence of malignant tumors in multiple experiments in male and female rats.

IARC (1997) has identified long palygorskite fibers (>5μm in length) as a Group 2B carcinogen based on sufficient evidence in experimental animals. The relevant studies are summarized below.

In studies by Wagner *et al.* (1987), three groups of five-week old male and female Fischer 344 rats were treated with different palygorskite samples (suspended in saline) via a single intrapleural injection. Two of the groups were treated with fibers longer than 6 μm. After treatment, animals were allowed to live out their natural life span but were killed if moribund. Animals receiving palygorskite in which 0.5% of the fibers were longer than 6 μm had a statistically significant increase in pleural mesotheliomas (14/40 rats). In animals injected with a sample in which 20% of the fibers were longer than 6 μm, 30/32 had pleural mesotheliomas. The incidence in the third group in which no fibers were greater than 2 μm in length was 2/40; in saline control rats, the incidence was 1/40 and in rats treated with a positive control, the incidence was 19/39.

In a study by Pott *et al.* (1976), female Wistar rats received three intraperitoneal injections of palygorskite fibers (suspended in saline) at one-week intervals. Thirty percent of fibers were longer than 5 μm in length. The average survival time for palygorskite-treated rats was 46 weeks after the first injection. Of 34 treated rats, 77% developed malignant tumors of the abdominal cavity, 24 mesotheliomas and 2 sarcomas.

In another study by Pott *et al.* (1987), five-week old female Wistar rats received three intraperitoneal injections of palygorskite fibers in which 3% of fibers were $\geq$ 5 μm in length. Treated animals had a median life span of 109 weeks. Abdominal tumors (described as sarcoma, mesothelioma or carcinoma), excluding tumors of the uterus, were reported in 12/30 rats. The tumor rate in a positive control group was 27/32. In a negative control group treated with granular titanium dioxide, the incidence was 0/32.

Pyridine (CAS No. 110-86-1)

Increased incidence of malignant tumors in male and female mice.

NTP (1997b; 1997c) has concluded that there is clear evidence of carcinogenic activity of pyridine in male and female $B6C3F_1$ mice.

NTP (1997c) exposed male and female F344/N rats, male Wistar rats and male and female $B6C3F_1$ mice to pyridine in drinking water for two years. In both male and female mice, increased incidences of hepatocellular neoplasms were observed. Pyridine exposure of mice resulted in statistically significant increases in hepatocellular carcinoma (males: 15/50, 35/50, 41/49, 40/50 for control, low-, mid- and high-dose animals,

respectively; females: 13/49, 23/50, 33/50, 41/50) and in uncommon hepatoblastoma (males: 2/50, 18/50, 22/49, 15/50; females: 1/49, 2/50, 9/50, 16/50).

In male F344/N rats, an increase in renal tubule neoplasms, which exceeded historical control ranges, was observed in high-dose animals. Incidences in standard (simple sections) and extended (step sections) evaluations combined were 2/50, 3/48, 6/50, 10/49 (adenoma) and 2/50, 4/48, 6/50, 10/49 (adenoma or carcinoma). NTP (1997c) concluded that there was some evidence of the carcinogenicity of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms.

NTP (1997c) also concluded that there was equivocal evidence of carcinogenicity of pyridine in female F344/N rats based on an increased incidence of mononuclear cell leukemia (12/50; 16/50; 22/50; 23/50). NTP (1997c) concluded that there was equivocal evidence of carcinogenicity of pyridine in male Wistar rats based on an increased incidence of interstitial cell adenoma of the testis.

These findings were published in a draft technical report and were subsequently reviewed and accepted at the December 9-10, 1997 NTP Technical Review Subcommittee Meeting as reported in the *Summary Minutes* for that meeting (NTP, 1997b).

References

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