CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

Reproductive and Cancer Hazard Assessment Section
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The chemicals listed in the following table 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 the chemicals and the relevant references to the authoritative body publications are also given. A summary of the results of relevant carcinogenicity studies of these chemicals follows the table.

Chemical	CAS No.	Identity of chemical	Reference
1-Amino-2,4-dibromo-anthraquinone	81-49-2	An anthraquinone-derived vat dye, used for cotton, wool, and cellulose acetate.	NTP (1994a; 1994c)
C.I. Direct Blue 15	2429-74-5	Benzidine-based dye used for cellulose, leather, paper, cotton, silk, wool, as a tint for cinematographic film, and to stain biological materials.	IARC (1993)
C.I. Direct Blue 218	28407-37-6	Benzidine-based, copper chelated dye used for cellulose, acetate, nylon, silk, wool, tissue, papers and other textile goods.	NTP (1994b)
3,7-Dinitrofluoranthene	105735-71-5	Laboratory research chemical; incomplete combustion product of liquified petroleum gas, particulate emissions from diesel engines and kerosene heaters.	IARC (1996a)
3,9-Dinitrofluoranthene	22506-53-2	Laboratory research chemical; incomplete combustion product of liquified petroleum gas, particulate emissions from diesel engines and kerosene heaters.	IARC (1996a)
Nitrobenzene	98-95-3	Starting material used primarily in the production of aniline; solvent, constituent of soap and polishes, spray paints.	IARC (1996b)

Summarized below are the relevant carcinogenesis studies and conclusions for chemicals 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. Documents published by the National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC), two Proposition 65 authoritative bodies, were

the primary sources for the summary. The statements in bold reflect 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 chemicals 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.

1-Amino-2,4-dibromoanthraquinone (CAS No. 81-49-2)

Positive cancer bioassays in both sexes of two species, with multiple sites in both species.

The National Toxicology Program (NTP, 1994a; 1994c) has concluded that there is clear evidence of carcinogenic activity of 1-amino-2,4-dibromoanthraquinone in male and female F344/N rats in male and female $B6C3F_1$ mice.

NTP (1994a) administered 1-amino-2,4-dibromoanthraquinone to F344/N rats and $B6C3F_1$ mice in feed for two years. In rats, there were increased incidences of neoplasms in the liver, large intestine, kidney and urinary bladder. In both male and female rats, statistically significant increases in hepatocellular adenoma and carcinoma were observed. In males, the incidence of hepatocellular carcinoma was 1/50, 12/40, 55/59, and 46/50 for control, low-, mid- and high-dose groups, respectively. In females, the incidence was 0/50, 12/40, 57/60 and 45/48. Metastases were common, primarily to the lungs. A statistically significant increase in hepatocholangiocarcinoma was also observed in female rats (0/50, 0/40, 11/60, and 13/48). Statistically significant increases in tumors were observed in the large intestines of both males (adenoma: 0/50, 13/40, 51/59, 40/50; carcinoma: 0/50, 1/40, 11/59, 17/50) and females (adenoma: 0/50, 28/40, 53/60, 43/49; carcinoma: 0/50, 2/40, 21/60, 8/49). In addition, in both male and female rats, there were statistically increased incidences of renal tubule adenoma (males: 2/50, 10/40, 11/59, 14/50; females: 0/50, 3/40, 16/60, 16/48) and transitional cell papilloma or carcinoma of the urinary bladder (males: 0/50, 1/38, 3/58, 12/50; females: 0/50, 2/40, 15/60, 25/46). In female rats, a dose-dependent increase in transitional cell carcinoma of the urinary bladder was observed (0/50, 0/40, 8/60, and 16/46).

In male and female $B6C3F_1$ mice, exposure to 1-amino-2,4-dibromoanthraquinone resulted in increased incidences of neoplasms in the liver, forestomach and lungs. In the liver, statistically significant increases in the incidences of both hepatocellular adenoma and carcinoma were observed. The incidence of hepatocellular adenoma or carcinoma was 18/50, 43/51, 42/50 (males) and 6/50, 46/50, 50/50 (females) for control, low- and high-dose groups, respectively. In the forestomach, statistically significant increases in squamous cell papilloma (males: 0/50, 13/51, 16/50; females: 2/50, 16/50, 27/50) and carcinoma (males: 0/50, 12/51, 13/50; females: 0/50, 12/50, 11/50) were observed. Alveolar/bronchiolar adenomas were also significantly increased in exposed males and females (males: 7/50, 26/51, 24/50; females: 4/50, 17/50, 13/49).

These findings were published in a draft technical report and were subsequently reviewed and accepted at the June 21, 1994 NTP Technical Review Subcommittee Meeting as reported in the *Summary Minutes* for that meeting (NTP, 1994c).

C.I. Direct Blue 15 (CAS No. 2429-74-5)

Positive cancer bioassays in male and female rats with significant tumor incidences at multiple sites.

IARC (1993) has identified C.I. Direct Blue 15 as a Group 2B carcinogen based on sufficient evidence in experimental animals.

NTP (1992) administered C.I. Direct Blue 15 to F344/N rats in drinking water for 96 weeks. Clear evidence of carcinogenicity was found in both male and female rats. Poor survival in the treated groups was due to the development of treatment related neoplasms. Exposure to C.I. Direct Blue 15 resulted in the increase of numerous tumors. There was a statistically significant increase in the incidence of skin basal-cell carcinoma/adenoma in males (2/50, 9/35, 27/65 and 28/50 for control, low-, mid- and high-dose groups, respectively) as well a significant increase in skin squamous-cell carcinoma/papilloma in both male and female rats (males: 2/50, 4/35, 11/65 and 19/50; females: 0/50, 2/35, 6/65, 5/50). Treatment also resulted in significant increases in the incidence of Zymbal's gland carcinoma/adenoma in both males and females (males: 1/50, 5/35, 10/65 and 20/50; females: 0/50, 4/35, 11/65, 17/50). In both male and female rats, there were significant increases in oral cavity squamous-cell carcinoma/papilloma (males: 1/50, 10/35, 24/65, 17/50; females: 2/50, 4/35, 19/65, 15/50). In addition, there was a significant increase in neoplasms of the large intestine in males (0/50, 1/35, 6/65, 8/50). There was a marked increase in clitoral gland adenoma/carcinoma in females (7/50, 11/31, 24/64, 27/50) and a significant increase in preputial gland tumors in mid-dose males (8/49, 5/35, 23/64, 9/48).

C.I. Direct Blue 218 (CAS No. 28407-37-6)

Positive cancer bioassays in male and female mice.

NTP (1994b) has concluded that there is clear evidence of carcinogenic activity of C.I. Direct Blue 218 in male and female $B6C3F_1$ mice based on increased incidences of hepatocellular adenomas and carcinomas.

NTP administered C.I. Direct Blue 218 to $B6C3F_1$ mice in feed for two years. In both males and females, statistically significant increases in the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma combined were observed. In males, the incidence of hepatocellular adenoma or carcinoma was 21/50, 20/50, 23/50 and 45/50 for control, low-, mid- and high-dose groups, respectively. In females, the incidence was 10/49, 15/50, 21/49, and 45/49. NTP noted that the strength of the carcinogenic response

was supported by the fact that the number of mice with multiple hepatocellular adenomas was also significantly increased in the high-dose groups (males: 31/50 compared to 4/50 in controls; females: 35/49 compared to 1/49 in controls). The incidence of hepatocellular adenoma or carcinoma in the high-dose groups exceeded the incidences of concurrent controls and the range for these neoplasms in the historical database.

NTP also administered C.I. Direct Blue 218 to male and female Fisher F344/N rats in feed for two years. NTP concluded that there was some evidence of carcinogenic activity in male rats based on a significantly increased incidence of squamous cell papilloma of the pharynx in high-dose males (0/50, 0/50, 0/50 and 5/50 for control, low-, mid-, and high- dose groups, respectively). The incidence exceeded the NTP historical incidence for this neoplasm in control male rats. In addition, a squamous cell carcinoma of the pharynx occurred in one high-dose male rat and another had a benign basosquamous tumor. No treatment-related tumors were observed in female rats.

3,7-Dinitrofluoranthene (CAS No. 105735-71-5)

Positive cancer bioassays in male rats.

IARC (1996a)[1] has identified 3,7-dinitrofluoranthene as a Group 2B carcinogen based on sufficient evidence in experimental animals. IARC previously considered this chemical in 1989. Newly available data were taken into consideration in the current evaluation. The relevant studies are briefly described below.

Tokiwa *et al.* (1987) administered 3,7-dinitrofluoranthene twice weekly to male Fischer 344/DuCrj rats by subcutaneous injection for 10 weeks, followed by a 50 week observation period. Animals with tumors at the site of injection were observed until moribund. All treated rats developed subcutaneous tumors within 48 weeks with 20/21 tumors identified as malignant fibrous histiocytomas; the first tumor was observed on day 155. Metastatic foci in the lungs were found in three animals. No subcutaneous tumors developed in the control animals.

Horikawa *et al.* (1991) exposed male Fischer 344/DuCrj rats to 3,7-dinitrofluoranthene via pulmonary implant. Animals were observed for up to 100 weeks. In the treated group, 12/22 animals developed lung tumors (11 squamous cell carcinomas); the earliest death caused by lung cancer occurred at week 50. No tumors were observed in control group animals.

IARC noted that 3,7-dinitroflouranthene was mutagenic in *Salmonella typhimurium* strains at extremely low doses. In mammalian cells, 3,7-dinitrofluoranthene induced chromosomal aberrations but not gene mutations. *In vivo*, 3,7-dinitrofluoranthene induced micronuclei in mouse bone marrow.

[1] This publication evaluates printing inks, carbon black and some nitro compounds. A review of additional information on carbon black is in progress.

3,9-dinitrofluoranthene (CAS No. 22506-53-2)

Positive cancer bioassays in male rats.

IARC (1996a) has identified 3,9-dinitrofluoranthene as a Group 2B carcinogen based on sufficient evidence in experimental animals. IARC previously considered this chemical in 1989. Newly available data were taken into consideration in the current evaluation. The relevant studies are briefly described below.

Tokiwa *et al.* (1987) administered 3,9-dinitrofluoranthene subcutaneously to male Fischer 344/DuCrj rats for 10 weeks. The animals were observed for 50 weeks; animals with tumors at the site of injection were observed until moribund. Ten of 11 treated rats developed malignant subcutaneous tumors within 48 weeks (7 malignant fibrous histiocytomas; 3 rhabdomyosarcomas). The earliest appearance of the tumor was on day 88. No subcutaneous tumors developed among the control animals.

Horikawa *et al.* (1991) exposed male Fischer 344/DuCrj rats to 3,9-dinitrofluoranthene via pulmonary implant. All animals were observed for up to 100 weeks. The earliest deaths caused by lung cancer in the 3,9-dinitrofluoranthene treated group were observed at weeks 99, 53, and 37 in the low-, mid- and high-dose groups, respectively. The incidence of lung cancer was 0/19, 1/10, 7/10, and 19/21 for control, low-, mid-, and high-dose groups, respectively. The tumors were primarily squamous cell carcinoma.

IARC reports that 3,9-dinitrofluoranthene is highly mutagenic to bacteria, particularly in the absence of an exogenous metabolic system. In mammalian cells, 3,9-dinitrofluoranthene induced chromosomal aberrations but not mutations. *In vivo*, 3,9-dinitrofluoranthene induced micronuclei in mouse bone marrow.

Nitrobenzene (CAS. No. 98-95-3)

Positive cancer bioassays in both sexes of mice and rats.

IARC (1996b) has identified nitrobenzene as a Group 2B carcinogen based on sufficient evidence in experimental animals.

Cattley *et al.* (1994) exposed male and female $B6C3F_1$ mice to nitrobenzene by inhalation to air containing nitrobenzene for 24 months. Exposure resulted in a statistically significant increase in the incidence of alveolar-bronchiolar adenomas and carcinomas in male mice (9/68, 21/67, 21/65, 23/66 for control, low-, mid-, and high-dose groups, respectively). There was also an increase in thyroid follicular-cell adenomas in treated males (0/65, 4/65, 1/65 and 7/64) and an increase in hepatocellular adenomas in high-dose females (6/51, 5/61, 5/64 and 13/62). Also in female mice, 5/60 high-dose animals developed mammary gland adenocarcinoma compared to 0/48 in controls.

Cattley *et al.* (1994) exposed male and female Fischer 344 rats to nitrobenzene by inhalation of air containing nitrobenzene for 24 months. Exposure resulted in significant increases in hepatic, renal and uterine neoplasms. The incidence of hepatocellular adenoma or carcinoma was 1/69, 4/69, 5/70, and 16/70 for control, low-, mid-, and high-dose groups, respectively for males and for females, 0/70, 2/66, 0/66, and 4/70. Renal tubular adenoma was increased in high-dose males (0/69, 0/68, 0/70 and 5/70); there was also one renal tubular carcinoma in high-dose males. In females, an increase in the incidence of endometrial stromal polyps (11/69, 17/6, 15/65, 25/69) was observed. There was also an increase in thyroid follicular-cell adenomas and adenocarcinomas in exposed males (2/69, 1/69, 5/70, 8/70).

Cattley *et al.* (1994) exposed male Charles River CD rats to nitrobenzene by inhalation of air containing nitrobenzene for 24 months. Exposure resulted in an increased incidence of hepatocellular adenoma or carcinoma in nitrobenzene exposed animals (2/63, 1/67, 4/70, 9/65 for control, low-, mid-, and high-dose groups, respectively).

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