CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

PACKAGE 19a
June 2, 2000

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

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), the U.S. Environmental Protection Agency (U.S. EPA), and the International Agency for Research on Cancer (IARC) are three of five institutions which have been identified as authoritative bodies for the purposes of Proposition 65 (22 CCR 12306(1)). One or more of these bodies has identified each of the chemicals in the table below as causing cancer. The Office of Environmental Health Hazard Assessment (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
Anthraquinone	84-65-1	Intermediate in manufacture of dyes and pigments; organic inhibitor; catalyst; additive in pulp and paper industry; accelerator in nickel electroplating.	NTP (1999a) NTP (1999d)
AZT (3'-azido-3'-deoxythymidine)	30516-87-1	Prescription drug used in treatment of AIDS	NTP (1999b) IARC (2000)
Bromate ion and its water soluble salts	-------	Chemical by-product, produced by ozonation of water containing bromide.	U.S. EPA (1998)
Bromoethane	74-96-4	Intermediate in organic synthesis, in manufacture of pharmaceuticals and in ethylation of gasoline. Also, fruit and grain fumigant[1], refrigerant and solvent.	NTP (1989a)
Diuron	330-54-1	Substituted urea herbicide used against broadleaf and grass weeds and mosses.	U.S. EPA (1997a)
Fumonisin B_1	116355-83-0	Mycotoxin, produced by fungus *Fusarium moniliforme*, found in corn and corn-based products.	NTP (1999c) NTP (1999d)
Isoxaflutole	141112-29-0	Experimental herbicide used for control of grasses and broadleaf weeds in field corn[2].	U.S. EPA (1997b)
Methyleugenol	93-15-2	Flavoring agent in jellies, baked goods, nonalcoholic beverages, chewing gum, candy, pudding, relish and ice cream; fragrance in perfumes, creams, lotions, detergents and soaps.	NTP (1998a) NTP (1998b)

[1] Never registered for use as a fumigant in California.
[2] Not registered for use in California.

Anthraquinone (CAS No. 84-65-1)

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

The National Toxicology Program (NTP, 1999a; 1999d) has concluded that there is clear evidence of the carcinogenic activity of anthraquinone in male and female $B6C3F_1$ mice and in female F344/N rats.

NTP (1999a) exposed $B6C3F_1$ mice and F344/N rats to anthraquinone via diet for two years. In male mice, anthraquinone exposure resulted in statistically significant dose-dependent increases in the incidences of hepatocellular adenoma (21/50, 32/50, 38/50, 41/49 for control, low-, mid- and high-dose animals, respectively), hepatocellular

carcinoma (8/50, 13/50, 17/50, 21/49) and hepatoblastoma (1/50, 6/50, 11/50, 37/49). Statistically significant increases in hepatocellular neoplasms were also observed in female mice. The incidence of hepatocellular carcinoma was 2/49, 3/50, 8/50, 8/49 for control, low-, mid-, and high-dose females, respectively. The combined incidence of hepatocellular adenoma or hepatocellular carcinoma in these groups was 6/49, 30/50, 30/50, and 41/49, respectively.

In female rats, anthraquinone exposure resulted in a statistically significant increase in combined renal tubule adenoma or carcinoma. The incidence was 0/50, 6/50, 9/50, 8/50 and 14/49 for control, low-, mid-, midhigh- and high-dose animals, respectively. The historical control incidence of these tumors in female rats in recent NTP feed studies was 1/901. The NTP (1999a) also concluded that observed increases in the incidences of urinary bladder transitional epithelial papilloma or carcinoma (combined) and of hepatocellular adenoma were related to anthraquinone exposure. In male rats, increases in renal tubule adenomas were also observed at all doses (1/50, 3/50, 9/50, 5/50, 3/50) but were only significant in the mid-dose group. The historical control incidence of this tumor type in male rats in recent NTP feed studies was 7/902. Transitional epithelial papillomas of the urinary bladder occurred in all groups of exposed males and were significant in the midhigh-dose group. The NTP (1999a) concluded that there was some evidence of carcinogenic activity of anthraquinone in male F344/N rats.

The NTP (1999a) also found that anthraquinone was mutagenic in *Salmonella typhimurium* strains TA98 and TA100, and although results of an acute exposure mouse bone marrow micronucleus test were negative, anthraquinone induced micronuclei in peripheral blood erythrocytes in mice after 14 weeks of exposure in feed. The NTP also noted that many substituted anthraquinones have also been carcinogenic in long-term animal studies.

The above findings were published in a draft technical report and were subsequently reviewed by an external advisory committee in a public meeting and accepted at the May 21, 1999 NTP Technical Reports Review Subcommittee Meeting, as reported in the *Summary Minutes* for that meeting (NTP, 1999d).

AZT [3'-azido-3'-deoxythymidine] (CAS No. 30516-87-1)

Increased incidence of malignant and combined malignant and benign tumors in female mice to an unusual degree with regard to site of tumor.

The National Toxicology Program (NTP, 1999b) has concluded that there is clear evidence of the carcinogenic activity of AZT (3'-azido-3'-deoxythymidine) in female $B6C3F_1$ mice. The International Agency for Research on Cancer (IARC, 2000) has also identified AZT as a group 2B carcinogen based on sufficient evidence for the carcinogenicity of AZT in experimental animals and inadequate evidence in humans.

NTP (1999b) administered AZT in 0.5% methylcellulose to male and female $B6C3F_1$ mice by gavage for two years. In female mice, there was a statistically significant increase in the incidence of squamous cell carcinoma of the vagina in mid- and high-dose animals (0/50, 0/50, 5/45 and 9/49 for control, low-, mid- and high-dose groups, respectively). Squamous cell carcinoma of the vagina has not been observed in any control female mouse in the current NTP historical database (for methylcellulose gavage studies, n=200). The combined incidence of squamous cell carcinoma or papilloma of the vagina was significantly increased in the two highest dose groups as well (0/50, 0/50, 5/45, 11/49). In additional experiments, NTP (1999b) administered a high or low dose of α-interferon (by subcutaneous injection) to $B6C3F_1$ mice receiving AZT. In animals receiving AZT plus interferon (low-dose), there was a statistically significant increase in squamous cell carcinoma of the vagina (0/49, 0/44, 5/48, 6/48). For mice receiving AZT plus the high-dose interferon treatment, increases in squamous cell carcinoma of the vagina were also significantly increased for the two highest dose groups (0/50, 0/48, 5/48, 4/50). Vaginal tumors were not observed in animals treated with either low- or high-dose interferon alone. In each of the AZT studies, a dose-dependent increase in epithelial hyperplasia of the vagina was also observed. No treatment-related tumors were observed in male mice.

The NTP (1999b) noted that these results were similar to those of Ayers *et al.* (1996) in which vaginal neoplasms were observed in AZT-exposed CD rats and CD-1 mice. In mice, squamous cell carcinomas of the vagina were observed in 5/60 females treated with high-dose AZT; squamous cell papillomas of the vagina were observed in 1/60 mid-dose and 1/60 high-dose animals. In the rat study, squamous cell carcinomas of the vagina were observed in 2/60 AZT-treated females.

IARC (2000) also evaluated a study in which transplacental administration of AZT resulted in an increased incidence and multiplicity of lung and liver tumors and an increased incidence of female reproductive tract tumors.

AZT is mutagenic *in vitro* and *in vivo*. NTP (1999b) reported that AZT induced gene mutations in *Salmonella typhimurium* strain TA102, with and without S9 activation. No increases in mutations were found in several other tested strains. In cytogenetic tests with cultured CHO cells, AZT induced sister chromatid exchanges, but not chromosomal aberrations, with and without S9 activation. The NTP (1999b) reported that *in vivo*, AZT markedly increased the frequency of micronucleated erythrocytes in bone marrow and in peripheral blood.

<u>Bromate ion and its water soluble salts</u>

Increased incidence of malignant and combined malignant and benign tumors in male and female rats; in males, tumors were observed at multiple sites in multiple experiments.

In 1993, the U.S. Environmental Protection Agency (U.S. EPA, 1993) classified bromate as a Group B2 carcinogen. In a 1998 Health Risk Assessment, U.S. EPA (U.S. EPA, 1998) stated, "Bromate should be evaluated as a likely human carcinogen by the oral route of exposure" and that the carcinogenicity of bromate in animals was demonstrated by three key sets of studies. These studies are described below.

In the first study (Kurokawa *et al.,* 1986a), male F344 rats were treated with water containing potassium bromate for 104 weeks. There were statistically significant increases in tumors at multiple sites. The combined incidences of adenoma and carcinoma of the kidney were significantly increased in animals in the two highest of six dose groups ($p < 0.001$ and $p < 0.05$ for the highest and next highest dose groups, respectively). Thyroid follicular cell adenomas and carcinomas combined were significantly increased in the high-dose group ($p < 0.05$) as were peritoneal mesotheliomas ($p < 0.05$). In the second set of studies (Kurokawa *et al.,* 1986b), bromate ion was administered in drinking water to male and female F344 rats and female $B6C3F_1$ mice. In male rats, there were statistically significant increases in renal carcinoma (3/53, 24/53, and 44/52 for control, low- and high-dose groups, respectively), combined renal adenomas and carcinomas (3/53, 32/53, 46/52), and peritoneal mesotheliomas (6/53, 17/52, 28/46). In female rats, statistically significant increases in renal carcinoma (0/47, 21/50, 36/49) and renal adenomas and carcinoma combined (0/47, 28/50, 39/49) were observed. Results in mice were inconclusive.

In the third set of studies (DeAngelo *et al.,* 1998), potassium bromate was administered to male F344 rats and male $B6C3F_1$ mice in drinking water for 100 weeks. In treated male rats, statistically significant increases in renal tumors (carcinomas: 0/45, 0/43, 2/47, 1/39, 4/32; combined adenomas/carcinomas: 1/45, 1/43, 6/47, 3/39, 12/32); thyroid tumors (carcinomas: 0/36, 2/39, 0/43, 2/35, 6/30; combined adenomas/carcinomas: 0/36, 4/39, 1/43, 4/35, 14/30); and testicular mesotheliomas (0/47, 4/49, 5/49, 10/47, 27/43) were observed. Mice appeared to be less sensitive than rats to the effects of bromate exposure. In male mice, kidney tumors were observed but the incidence was not dose-dependent. U.S. EPA (1998) also noted that bromate ion has been found to be mutagenic in both *in vitro* and *in vivo* assays.

In all of the cited studies, bromate ion was administered as potassium bromate. Potassium bromate was listed as causing cancer under Proposition 65 on January 1, 1990. Potassium bromate is readily soluble in water. At drinking water pH, it (and other water soluble bromate salts) should exist almost exclusively in the ionic form. Thus, U.S. EPA (1993 and 1998) refers to dose of bromate in its documents and characterizes the potential for carcinogenicity following bromate ion exposure.

Bromoethane (CAS No. 74-96-4)

Increased incidence of malignant and combined malignant and benign tumors in female mice to an unusual degree with regard to site and incidence.

NTP (1989a) has concluded that there is clear evidence of the carcinogenic activity of bromoethane in female mice.

NTP (1989a) exposed F344/N rats and B6C3F_1 mice of both sexes to bromoethane via inhalation for two years. In female mice, a dose-dependent increase in endometrial uterine adenocarcinoma (0/50, 2/50, 3/47, and 19/48 for control, low-, mid- and high-dose groups, respectively) was observed in bromoethane-exposed animals. Squamous cell carcinoma of the uterus was also observed (0/50, 1/50, 1/47, 3/48). The combined incidence of adenoma, adenocarcinoma or squamous cell carcinoma of the uterus was 0/50, 4/50, 5/47, and 27/48. NTP reported the historical incidence of adenoma or adenocarcinoma of the uterus in the study laboratory as follows: nonchamber controls, 5/2,011; chamber controls, 4/335. For squamous cell neoplasms of the uterus, the historical control incidence was reported as 0/335 in chamber controls and 1/2,011 in controls from noninhalation studies.

In male mice, the incidence of alveolar/bronchiolar tumors was significantly increased in the high-dose group. However, the incidence was within the range of historical controls and there was no evidence of an increased incidence of hyperplasia in support of the finding of neoplasia. NTP concluded there was equivocal evidence for the carcinogenic activity of male B6C3F_1 mice.

NTP also concluded there was some evidence for the carcinogenic activity in male rats based on a significant increase in the incidence of adrenal pheochromocytomas (8/40, 23/45, 18/46, 21/46). No treatment related tumors were observed in female rats.

The NTP noted that in a separate study, inhalation of the structurally related compound chloroethane also resulted in an increased incidence of uterine carcinomas (0/49 for control and 43/50 for chloroethane-treated animals) in female B6C3F_1 mice (NTP, 1989b). Although the incidence of malignant tumors and the number of metastasizing tumors was lower in the bromoethane-treated mice compared to the chloroethane treated mice, the doses used in the bromoethane studies were markedly lower (100, 200 or 400 ppm in the bromoethane studies compared to15,000 ppm in the chloroethane studies). Chloroethane was listed as causing cancer under Proposition 65 in 1990 via the authoritative bodies mechanism on the basis of the NTP report. In 1991 and once again in 1999, IARC evaluated bromoethane and chloroethane and based on IARC's criteria, concluded that there was limited evidence of carcinogenicity in experimental animals in each case.

Diuron (CAS No. 330-54-1)

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

U.S. EPA (1997a) has concluded that diuron is "known/likely" to be carcinogenic to humans by all routes of exposure based on studies in Wistar rats and in NMRI mice. The studies are briefly summarized below.

Diuron was administered to male and female Wistar rats via diet for two years. Marked increases in urinary bladder epithelial carcinomas and combined papillomas and/or carcinomas were observed in the high-dose groups of both sexes. The incidence of urinary bladder epithelial carcinomas in male rats was 1/49, 0/50, 1/49, and 35/48 (for control, low-, mid- and high-dose groups, respectively) and in female rats, 1/47, 0/49, 1/50, and 13/49. Male rats also had a significant increasing trend in kidney renal pelvis epithelial papillomas and/or carcinomas. Two kidney carcinomas, considered a rare tumor, were observed in high-dose male rats.

Male and female NMRI mice were exposed to diuron via the diet for 24 months. In females, increases in the incidence of mammary gland adenocarcinomas (2/34, 1/29, 1/44, 6/37) occurred with a significant positive trend. The incidence of mammary gland adenocarcinomas at the highest dose exceeded historical controls from the testing laboratory. Of the 16 studies in the historical control database from the testing laboratory, the highest number of female mice with malignant mammary gland tumors in any of these 16 control groups was three and was observed in three separate studies (3/48, 3/48, 3/49). No treatment related tumors were observed in male mice.

Fumonisin B_1 (CAS No. 116355-83-0)

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

The National Toxicology Program (NTP, 1999c; 1999d) has concluded that there is clear evidence of the carcinogenic activity of fumonisin B_1 in male F344/N rats and in female $B6C3F_1$ mice.

NTP (1999c) exposed $B6C3F_1$ mice and F344/N rats to fumonisin B_1 via diet for two years. In male rats, statistically significant increases in renal tubule adenoma and in renal tubule carcinoma were observed. The incidence of renal tubule carcinoma was 0/48, 0/40, 0/48, 7/48, and 10/48 for control, low-, mid-, midhigh- and high-dose groups, respectively. The combined incidence of renal tubule adenoma or carcinoma was 0/48, 0/40, 0/48, 9/48, and 15/48. No neoplastic effects were seen in female rats exposed to fumonisin B_1. The NTP (1999c) commented that "it appears that female rats could have tolerated somewhat higher exposure concentrations."

In treated female mice, increased incidences of hepatocellular adenoma (5/47, 3/48, 1/48, 16/47, 31/45), hepatocellular carcinoma (0/47, 0/48, 0/48, 10/47, 9/45) and combined hepatocellular adenoma or carcinoma (5/47, 3/48, 1/48, 19/47, 39/45) were observed. The increases were statistically significant at the two highest dose levels. The NTP (1999c) found that decreased survival in the highest dose group was probably due to the increased incidence of hepatocellular neoplasms. No increases in tumor incidence were observed in male mice.

These findings were published in a draft technical report and were subsequently reviewed by an external advisory committee in a public meeting and accepted at the May 21, 1999 NTP Technical Reports Review Subcommittee Meeting, as reported in the *Summary Minutes* for that meeting (NTP, 1999d).

Isoxaflutole (CAS No. 141112-29-0)

Increased incidence of malignant and combined malignant and benign liver tumors in mice and rats of both sexes with early onset of tumors in male mice. There was also an increased incidence of malignant and combined malignant and benign thyroid tumors in male rats.

U.S. EPA (1997b) concluded that isoxaflutole is "likely to be a human carcinogen" by all routes of exposure. This conclusion was based on statistically significant increases in liver tumors in both sexes of mice and rats with an early onset in male mice. There were also statistically significant increases in thyroid tumors in male rats. The studies considered by U.S. EPA (1997b) are discussed below.

Male and female mice were exposed to isoxaflutole via diet for 78 weeks. A small group of animals was sacrificed at 53 weeks. At the 53-week interim sacrifice, the incidence of hepatocellular adenomas in high-dose male mice (7/12) was significantly greater than that in control mice (2/12), providing evidence of early onset of adenomas. In addition, the first liver carcinoma in treated male mice was observed at week 47. At 78 weeks, statistically significant increases in hepatocellular adenomas, carcinomas, and adenomas or carcinomas combined were observed in both male and female mice. Excluding the 53-week interim sacrifice animals, the incidence of hepatocellular carcinoma in male mice was 4/47, 5/50, 8/48, and 17/49 (for control, low-, mid- and high-dose groups, respectively) and in female mice, 0/51, 0/50, 0/48, and 4/51. The combined incidence of hepatocellular adenoma or carcinoma in male mice was 13/47, 15/50, 14/48, and 38/49; the incidence in female mice was 0/51, 1/50, 1/48, and 18/51.

In the rat carcinogenicity studies, male and female Sprague-Dawley rats were exposed to isoxaflutole via diet for 104 weeks. Statistically significant increases in hepatocellular adenomas and carcinomas were observed in both male and female rats. The incidence of carcinoma was 5/58, 1/53, 4/62, 2/64, and 17/68 in male rats and 0/70, 0/71, 1/69, 0/66, and 24/73 in female rats. The combined incidence of hepatocellular adenoma or carcinoma was 7/58, 4/53, 8/62, 8/64, and 31/68 for male rats and 4/70, 2/71, 2/69, 0/66,

and 46/73 for female rats. The incidence of thyroid tumors was also increased in male rats. The incidences of thyroid follicular cell adenomas and carcinomas combined were significantly greater in high-dose rats than in control rats (combined adenomas or carcinomas: 3/66, 2/60, 7/69, 8/68, 17/69).

Methyleugenol (CAS No. 93-15-2)

Increased incidence of malignant and combined malignant and benign tumors in mice and rats of both sexes with tumors at multiple sites in male and female rats and male mice.

NTP (1998a; 1998b) has concluded that there is clear evidence of the carcinogenic activity of methyleugenol in male and female F344/N rats and in male and female $B6C3F_1$ mice.

NTP (1998a) treated F344/N rats and $B6C3F_1$ mice with methyleugenol by gavage five days per week for two years. In rats, statistically significant increases in tumors at multiple sites were observed in treated animals of both sexes. The incidence of hepatocellular carcinoma was 2/50, 3/50, 14/50, 25/50, and 36/50 for vehicle control, low-, mid-, mid-high and high-dose male rats, respectively and 0/50, 0/50, 4/49, 8/49, and 22/50 for female rats. The combined incidence of hepatocellular adenoma or carcinoma was 7/50, 14/50, 28/50, 43/50, and 45/50 in male rats and 1/50, 8/50, 14/49, 34/49, and 43/50 in female rats. The combined incidence of hepatocholangioma and hepatocholangiocarcinoma was 0/50, 0/50, 1/50, 2/50, and 13/50 in male rats and 0/50, 0/50, 0/49, 3/49, and 17/50 in female rats. The incidence of tumors of the glandular stomach was also greater in treated rats of both sexes than in vehicle controls. In male rats, the incidence of malignant mesothelioma was 1/50, 3/50, 5/50, 12/50, and 5/50, which was significantly greater in the two highest dose groups compared to the vehicle control group. There were also statistically significant increases in the incidences of mammary gland fibroadenoma at the mid-dose levels (5/50, 5/50, 15/50, 13/50, 6/50) and in renal tubule adenoma at the three highest dose levels (extended and standard evaluation combined: 4/50, 6/50, 17/50, 13/50, 20/50) in male rats.

In mice of both sexes statistically significant increases in liver tumors were observed in treated animals. The combined incidence of hepatocellular carcinoma and hepatoblastoma was 10/49, 20/50, 20/50, and 11/50 in male mice and 7/50, 38/50, 48/49, and 49/50 in female mice. The combined incidence of hepatocellular adenoma, carcinoma or hepatoblastoma was 31/49, 47/50, 46/50, and 41/50 in male mice and 25/50, 50/50, 49/49, and 49/50 in female mice. In addition, two malignant endocrine tumors of the glandular stomach were observed in two high-dose male mice. Because these neoplasms had not been previously observed in NTP gavage studies and because they were also observed in rats, these neoplasms were considered to be related to methyleugenol administration.

These findings were published in a draft technical report and were subsequently reviewed by an external advisory committee in a public meeting and accepted at the October 30, 1998 NTP Board of Scientific Counselors' Technical Reports Review Subcommittee Meeting, as reported in the *Summary Minutes* for that meeting (NTP, 1998b).

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