CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING VIA THE AUTHORITATIVE BODIES MECHANISM

PACKAGE 19b
September 29, 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
Catechol	120-80-9	Used as a starting material for insecticides, perfumes, drugs and polymerization inhibitors; also as an antiseptic, in photography, dyestuffs, electroplating, specialty inks, antioxidants and light stabilizers, and in organic synthesis.	IARC (1999a)
DEF (S,S,S-tributyl phosphorotrithioate; Tribufos)	78-48-8	Organophosphate insecticide used on cotton, with minor use reported on dried beans.	U.S. EPA (1997c)
Ethoprop	13194-48-4	Organophosphate nematocide used primarily on potatoes and sweet potatoes.	U.S. EPA (1997a)
Indium phosphide	22398-80-7	Used in microelectronics industry to make semiconductors, injection lasers, solar cells, photodiodes and light-emitting diodes.	NTP (2000a; 2000c)
Lynestrenol	52-76-6	Progestogen used in oral contraceptive pills and in treatment of dysfunctional uterine bleeding and endometriosis.	IARC (1999b)
Naphthalene	91-20-3	Natural constituent of coal tar and crude oil; chemical intermediate in synthesis of phthalic and anthranilic acids, naphthols, naphthylamines, and synthetic resins; ingredient in some moth repellants and toilet bowl deodorants; used in veterinary medicine and as a bird repellant[1].	NTP (2000b; 2000c)
Norethynodrel	68-23-5	Progestogen used in oral contraceptive pills; in treatment of dysfunctional uterine bleeding, endometriosis.	IARC (1999b)
Propachlor	1918-16-7	Herbicide used on corn, sorghum and onion seeds[1].	U.S. EPA (1997b)
Strong inorganic acid mists containing sulfuric acid	7664-93-9 (sulfuric acid)	Generated during a variety of manufacturing processes during which sulfuric acid is used or produced.	NTP (2000d)

[1]Not currently registered in California.

Catechol (CAS No. 120-80-9)

Increased incidences of malignant tumors in female rats, and of malignant and combined malignant and benign tumors in male rats of multiple strains.

IARC (1999a) has concluded that there is sufficient evidence for the carcinogenicity of catechol in experimental animals and has classified catechol in Group 2B, possibly carcinogenic to humans. The relevant studies evaluated by IARC are summarized below.

Hirose *et al.* (1990; 1993) treated Fischer 344 rats (30 rats/group/sex) with 0 or 0.8% catechol in the diet for 104 weeks. In the glandular stomach, adenocarcinomas were observed in 15/28 treated males and 12/28 treated females ($p<0.001$) compared with none in control animals.

Tanaka *et al.* (1995) administered catechol (0 or 0.8%) to male Wistar, WKY, Lewis and SD rats (20-30 animals/group). In treated animals, forestomach papillomas occurred in 6/30 SD rats, 2/30 Wistar rats and 1/30 WKY rats. Forestomach carcinomas were observed in 1/30 SD rats and 1/30 Wistar rats. No tumors were observed in control animals. In the glandular stomach, the incidence of adenomas was 97-100% in treated groups in all strains, compared with none in controls. Adenocarcinomas occurred in 23/30 SD rats, 22/30 Lewis rats, 20/30 Wistar rats and 3/30 WKY rats, compared to none in controls.

DEF [S,S,S-tributyl phosphorotrithioate; Tribufos] (CAS No. 78-48-8)

Increased incidence of malignant and combined malignant and benign tumors, including a rare malignant tumor, in male and female mice.

U.S. EPA (1997c) has concluded that DEF should be characterized as “likely” to be carcinogenic to humans at high doses, based on increases in tumors in male and female mice. The relevant studies are summarized below.

Male and female CD-1 mice were fed DEF via diet for 90 weeks. Adenocarcinomas of the small intestine were observed in both male and female mice (males: 0/50, 0/50, 0/50, and 9/50 for control, low-, mid- and high-dose groups, respectively; females: 0/50, 1/50, 0/50, 4/50). The incidence was statistically significant in high-dose males ($p<0.05$) and occurred with a positive trend in females ($p<0.01$, Mantel-Haenszel trend test performed by OEHHA). Adenocarcinoma of the small intestine is a rare tumor in CD-1 mice, and no tumors of this type have been observed in 150 male or 150 female CD-1 mice at the study laboratory. In male mice, an increase in hemangiosarcoma of the liver was also observed in mid- and high-dose animals (1/50, 1/50, 4/50, 7/50). The increase was

statistically significant in the high-dose group ($p<0.05$) and was outside the historical control range for male mice reported by the study laboratory (3/50, 0/50, 1/50 in three studies. Significant increases in alveolar/bronchiolar adenomas ($p<0.01$) were also observed in high-dose female mice (5/50, 5/50, 2/50, 15/50). The California Department of Pesticide Regulation (1999) noted, in their review of this study, that the combined incidence of alveolar/bronchiolar adenomas or carcinomas was also significantly greater than the control incidence ($p<0.01$). No treatment related tumors were observed in Fischer 344 rats administered DEF via diet for 24 months.

The U.S. EPA classification was summarized in a 1999 Human Health Risk Assessment of DEF. In the 1999 risk assessment, U.S. EPA (1999a) states that DEF was classified as a "likely human carcinogen" at high doses, based on increases in tumors in: both sexes of the CD-1 mouse; the liver of male mice; in the lung of female mice; and in the small intestine in both sexes of mice.

Ethoprop (CAS No. 13194-48-4)

Increased incidence of a rare malignant tumor in male rats; increased incidence of malignant and combined malignant and benign tumors in two strains of male rats.

U.S. EPA (1997a) has concluded that the organophosphate ethoprop is a "likely" human carcinogen based on studies in two strains of rats and on evidence of the clastogenicity of ethoprop in *in vitro* mutagenicity testing. The relevant animal studies are briefly summarized below**.**

In one study, ethoprop was administered via diet to male and female Sprague-Dawley rats (70 rats/group/sex) for two years. Male rats had a significant increasing trend ($p<0.01$) for malignant pheochromocytoma of the adrenal gland, a rare life-threatening tumor in Sprague-Dawley rats. This tumor type was seen in all doses tested. The incidence was significantly increased ($p<0.01$) in high-dose animals (0/41, 2/16, 2/18, and 5/60 for control, low-, mid- and high-dose groups, respectively), occurred with a significant positive trend ($p<0.01$) and exceeded the historical control range (0 – 1.7%). In the low- and mid-dose groups, the adrenals were examined in relatively few animals; therefore, the true tumor incidence at these doses was not determined. U.S. EPA (1997a) noted that tumors were also seen in the low-dose group where cholinesterase inhibition did not occur.

Male rats in this study also had an increasing trend ($p<0.05$) for thyroid C-cell carcinomas (0/61, 0/63, 1/64, 3/66). The incidence in the high-dose group was significantly increased compared to control animals ($p<0.05$) and also exceeded the historical control range. Of the seven studies conducted at the testing laboratory, C-cell carcinomas were observed in 1/50 (2%) rats in one study and 1/60 (1.7%) rats in another study and none in five other

studies consisting of 330 rats in total. U.S. EPA (1997a) wrote: "Thus, the incidence (5%) of this tumor seen in the present study was more than twice that seen in seven previous studies."

In another study, male and female F344 rats were exposed to ethoprop via diet for two years. An increase in C-cell tumors of the thyroid was observed in male rats with significant increasing trends for C-cell carcinomas (0/49, 0/48, 1/50, 3/50; $p<0.05$), adenomas (8/49, 5/48, 5/50, 12/50; $p<0.05$), and combined adenomas/carcinomas (8/49, 5/48, 6/50, 15/50; $p<0.01$). Historical control data was not provided by the study laboratory. However, thyroid C-cell adenomas and carcinomas exceeded the historical control range from other laboratories. Female rats had no statistically significant increase in tumors.

In an additional study with Fischer 344 rats, animals were exposed to ethoprop *in utero*, by lactation and by feeding. In male rats, thyroid C-cell adenomas (2/46, 4/43, 1/41, 10/40) occurred with a significant increasing trend ($p<0.01$), and tumor incidence was significantly greater in the high-dose group compared to the control group ($p<0.01$). Although only adenomas were seen in this study, U.S. EPA (1997a) considered the presence of C-cell tumors supportive of the studies discussed above.

U.S. EPA (1997a) also considered that ethoprop exhibited clastogenic activity *in vitro* in the presence of metabolic activation. U.S. EPA (1997a) wrote: "This activity provided support for a mutagenic component of the carcinogenicity concern."

The carcinogenicity classification of ethoprop was discussed in a 1999 Human Health Risk Assessment of ethoprop (U.S. EPA, 1999b). In the 1999 risk assessment, U.S. EPA states that ethoprop was classified as a "likely" human carcinogen due to the occurrence of malignant adrenal pheochromocytomas in male Sprague-Dawley rats and that "[t]his classification was supported by the occurrence of thyroid C-cell adenomas and/or carcinomas in three different rat studies and evidence of clastogenicity by *in vitro* mutagenicity testing." U.S. EPA (1999b) also reported that the carcinogenicity of ethoprop was re-evaluated in 1998. The Health Effects Division Cancer Assessment Review Committee concluded again that ethoprop should be classified as a "likely" human carcinogen.

Indium phosphide (CAS No. 22398-80-7)

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

The National Toxicology Program (NTP, 2000a) has concluded that there is clear evidence of the carcinogenic activity of indium phosphide in male and female F344/N rats and in male and female $B6C3F_1$ mice.

The NTP (2000a) exposed male and female F344/N rats and $B6C3F_1$ mice to particulate aerosols of 0.03, 0.1, or 0.3 mg/m^3 indium phosphide in studies initially designed to run 105 weeks. Because of significant increases in lung weight and a spectrum of proliferative and inflammatory lesions in the mid- and high-dose groups, exposure to indium phosphide was terminated at 21 weeks for these groups (in both mice and rats). These animals continued unexposed in chambers until the end of the respective studies. Animals exposed to the low-dose indium phosphide continued at this dose for the duration of the studies as lung weights were increased to a lesser extent and lung lesions were considered minimal (rats) or minimal to mild (mice). Because exposure was stopped for the mid- and high-dose groups, the timing and the extent of exposure differed for these two groups compared to the low-dose group. The NTP (2000a) estimated that animals receiving the mid-dose (0.1 mg/m^3) indium phosphide had the lowest exposure of the three dose levels.

In rats, tumors were observed in the lung and the adrenal medulla. In male rats, there was a statistically significant increase in alveolar/bronchiolar carcinoma at all dose levels (1/50, 10/50, 8/50, and 16/50 for control, low-dose, mid-dose (stop-exposure), and high-dose (stop-exposure) groups, respectively). The combined incidence of alveolar/bronchiolar adenoma or carcinoma (7/50, 22/50, 30/50 and 35/50) was significantly increased in all dosed animals ($p<0.001$). There was also an increase in squamous cell carcinoma of the lung (0/50, 0/50, 0/50, 4/50; $p=0.01$, Poly-3 trend test). The historical control incidence for this tumor type in male F344 rats is 0/299. The incidence of benign, complex or malignant pheochromocytoma (10/50, 26/50, 18/49, 24/50) was significantly increased in low-dose [$p<0.001$] and high-dose (stop-exposure)[$p=0.003$] male rats.

In female rats, the incidence of alveolar/bronchiolar carcinoma was significantly increased ($p=0.002$) in the high-dose (stop-exposure) group (1/50, 3/50, 1/50, 11/50; $p<0.001$, Poly-3 trend test). The incidence of alveolar/bronchiolar adenoma or carcinoma (1/50, 10/50, 6/50, 26/50; $p<0.001$, Poly-3 trend test) was also significantly greater in low-dose [$p=0.004$] and high-dose (stop-exposure) [$p<0.001$] animals compared to control animals. In female rats, the incidence of benign or malignant pheochromocytoma

was significantly increased in the high-dose (stop-exposure) [p = 0.026] group (2/50, 6/48, 2/50, 9/49; p=0.005, Poly-3 trend test).

In mice, the incidence of alveolar/bronchiolar carcinoma was significantly increased in all groups of exposed males (6/50, 15/50, 22/50, and 13/26 for control, low-dose [p=0.008], mid-dose (stop-exposure) [p<0.001], and high-dose (stop-exposure) [p=0.042] groups, respectively) and in females in the low-dose [p=0.029] and high-dose (stop-exposure) [p=0.016] groups (1/50, 6/50, 5/50, 7/50). The combined incidence of alveolar/bronchiolar adenoma or carcinoma was significantly increased (p<0.05) for all groups of treated females (4/50, 11/50, 15/50, 14/50; p=0.006, Poly-3 trend test)). In discussing lung tumors in mice, the NTP (2000a) stated: "The neoplastic responses in the lungs of mice are even more significant than those in rats, because mice are generally not responsive to particulate exposure for the development of lung neoplasms even at high exposure concentrations."

Liver tumors were also observed in both male and female mice. The incidence of hepatocellular carcinoma in male mice was significantly increased in low-dose [p=0.014] and in mid-dose (stop-exposure) [p=0.010] animals (11/50, 22/50, 23/50, 16/50). The combined incidence of hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma was significantly increased (p<0.02) for all dosed groups (26/50, 40/50, 37/50, 39/50; p=0.003, Poly 3-trend test). In female mice, the incidence of hepatocellular carcinoma was significantly greater in low-dose animals (17/50; p<0.001) than in control animals (6/50).

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 18, 2000 NTP Technical Reports Review Subcommittee Meeting, as reported in the *Summary Minutes* for that meeting (NTP, 2000c).

<u>Lynestrenol (CAS No. 52-76-6)</u>

Increased incidence of malignant tumors in multiple species.

IARC (1999b) has concluded that there is sufficient evidence for the carcinogenicity of lynestrenol in experimental animals. Lynestrenol was previously evaluated by IARC in 1979. Previously reviewed studies were noted in the 1999 evaluation and are briefly reviewed below together with the newly evaluated studies.

Misdorp (1991) treated pure-bred female beagle dogs with daily oral tablets of lynestrenol at doses representing 10, 50 and 125 times the human contraceptive dose for 364 weeks. At the lowest dose, lynestrenol appeared to protect against the development of mammary tumors; at intermediate and high doses, lynestrenol was associated with increased

incidences of mammary nodules and carcinomas. The results from this study are summarized below:

Effects of lynestrenol on mammary tumor incidence in female beagle dogs [from Misdorp (1991)].

Treatment	Nodule Incidence	Nodule latency (weeks)	Carcinoma Incidence
Control	5/16	323	1/16
10 x HCD	0/16*		[0]
50 x HCD	16/16	191**	3/16
125 x HCD	16/16	152**	7/16***

HCD, human contraceptive dose
* Significantly lower than in other groups ($p<0.05$)
**Significantly earlier than in controls ($p<0.05$)
***Significantly greater than control group ($p<0.05$) using the Fisher exact test (performed by OEHHA)

In studies evaluated previously by IARC (1979) and summarized in the 1999 monograph, lynestrenol treatment resulted in a slight increase in tumor incidence. In one study, male and female Swiss random-bred mice (114-123/dose group) were treated with lynestrenol alone or in combination with the estrogen mestranol (33:1) via diet for 80 weeks. In female mice, the incidence of malignant mammary tumors increased to 4% in mice fed lynestrenol alone and 6% in mice fed the combination; the incidence in control mice was 0/47. In another study, female rats (189/dose group) treated with lynestrenol had a slightly increased incidence of malignant mammary tumors (3% compared to 0/114 controls) [Committee on Safety of Medicines, 1972].

Schuppler and Gunzel (1979) also summarized a study in which male and female mice were treated orally with lynestrenol for 20 months. In males, there was a significant increase in the incidence of hepatocellular adenomas, from approximately 1 to 8% ($p<0.05$).

<u>Naphthalene (CAS No. 91-20-3)</u>

Increased incidence of a rare malignant tumor in male and female rats.

The NTP (2000b) has concluded that there is clear evidence of the carcinogenic activity of naphthalene in male and female F344/N rats.

The NTP (2000b) exposed male and female F344/N rats to naphthalene by inhalation for two years. Neuroblastoma of the nasal olfactory epithelium, a rare malignant tumor in

rodents, was observed in both male and female rats. In female rats, neuroblastomas of the olfactory epithelium were observed in all exposed groups (0/49, 2/49, 3/49 and 12/49 for control, low-[p=0.214], mid-[p=0.112], and high-dose [p<0.001] groups, respectively; p<0.001, Poly-3 trend test), and were significantly increased in high-dose animals. In male rats, the incidence of neuroblastomas of the olfactory epithelium was also increased (0/49, 0/49, 4/48 [p=0.056], 3/48 [p=0.109]) and occurred with a positive trend (p=0.027). Neuroblastomas have not been observed in male or female chamber control rats in the NTP historical database (for animals fed NIH-07 feed, 0/1048 (males) and 0/1044 (females); for animals fed NTP-2000 feed, 0/299 (males) and 0/299 (females)).

Statistically significant increases (p<0.01) in adenomas of the nasal respiratory epithelium were also observed in all exposed males (0/49, 6/49, 8/48, 15/48; p<0.001, Poly-3 trend test). In female rats, the incidence of adenomas of the nasal respiratory epithelium was also increased (0/49, 0/49, 4/49 [p=0.053], 2/49; p=0.066 Poly-3 trend test). This is also a rare neoplasm that has not been observed in NTP historical chamber control rats (for animals fed NIH-07 feed, 0/1048 (males) and 0/1044 (females); for animals fed NTP-2000 feed, 0/299 (males) and 0/299 (females)).

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 18, 2000 NTP Technical Reports Review Subcommittee Meeting, as reported in the *Summary Minutes* for that meeting (NTP, 2000c).

<u>Norethynodrel [CAS No. 68-23-5]</u>

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

IARC (1999b) has concluded that there is sufficient evidence for the carcinogenicity of norethynodrel in experimental animals. Norethynodrel was previously evaluated by IARC in 1979. Previously reviewed studies were noted in the 1999 evaluation and are briefly reviewed below along with the newly evaluated studies.

In one study, male and female CF-LP mice (120/group) were treated with norethynodrel, alone or in combination with mestranol (66:1 and 25:1), via diet for 80 weeks. In treated female mice, eight malignant mammary tumors were found, five of which occurred in mice that received the high dose of norethynodrel alone, compared with 4/240 in controls. Both norethynodrel alone or in the combinations resulted in an increased incidence of pituitary tumors in males and females. Pituitary tumors ranged from 2-8 tumors in control groups to incidences of 30-47 in treated groups, with most of the increases in the mid- and high-dose groups. (Committee on Safety of Medicines, 1972).

In another study, Rudali (1975) reported that norethynodrel increased the incidence of mammary tumors and decreased the latency period for tumor development in castrated male mice.

In rats, the Committee on Safety of Medicines (1972) reported an increase in pituitary, mammary and liver tumors in male and female rats (120/dose group) treated with norethynodrel, alone or in combination with mestranol (66:1 and 25:1). Of male rats receiving norethynodrel alone, 43% developed pituitary tumors compared to 6% of controls. No female rats receiving norethynodrel alone had pituitary tumors; however 20% of female rats fed 25:1 norethynodrel:mestranol developed tumors of the pituitary compared to 8% in controls. Both benign and malignant mammary tumors were seen in male rats given norethynodrel with or without mestranol (15-19% compared with 0 in controls). In female rats, the incidence of malignant tumors was increased only in rats fed 25:1 norethynodrel:mestranol (20%, compared with 7% in controls). IARC (1979) noted that the report stated that these increases occurred almost entirely in the high-dose group. Administration of norethynodrel alone also increased the incidence of benign liver-cell tumors in males from 3 to 24%, mostly in the mid- and high-dose groups. Malignant hepatomas occurred in 8% of males, mainly in animals receiving the medium and high doses. Female rats had much lower incidences of benign liver-cell tumors (<5%) and no malignant hepatomas. IARC (1999b), citing Schuppler and Gunzel's (1979) summary of the Committee on Safety of Medicines (1972) study, reported that oral administration of norethynodrel for two years resulted in statistically significant increases in hepatocellular adenomas in both mice and rats.

In another study, female $B6AF_1$ mice received an intrauterine exposure to the carcinogen 3-methylcholanthrene. Pellets of norethynodrel either alone or in combination with mestranol were then implanted subcutaneously and were renewed every three weeks for a total of 15 weeks. No tumors developed in mice that did not receive 3-methylcholanthrene. In pretreated mice, norethynodrel alone promoted the incidence of uterine tumors (11/14 compared with 5/35 in 3-methylcholanthrene-treated controls; $p<0.001$, Fisher's exact test, performed by OEHHA) [Blanzat-Reboud and Russfield, 1969].

Propachlor (CAS No. 1918-16-7)

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

U.S. EPA (1997b) has concluded that the herbicide propachlor is a "likely" human carcinogen by all routes of exposure. The relevant animal studies are briefly summarized below.

In one study, male and female Sprague-Dawley rats were administered propachlor in the diet for 104 weeks. The U.S. EPA (1997b) concluded that the dose levels tested in this study were not high enough to assess the carcinogenic potential of propachlor. However, at the doses tested, thyroid tumors were observed in both males and females and ovarian tumors were observed in female rats. In high-dose male rats, there was a statistically significant increase in the combined incidence of thyroid C-cell adenoma or carcinoma (1/50, 2/49, 2/49 and 6/47 for control, low-, mid- and high-dose [$p < 0.05$] groups, respectively). In female rats, there were significant positive trends for thyroid C-cell adenomas ($p < 0.05$) and combined adenomas and carcinomas ($p < 0.05$). There were also significant positive trends ($p < 0.01$) in female rats for ovarian granulosa/theca cell tumors (benign and combined benign or malignant). In high-dose females, the incidence of combined ovarian granulosa/theca cell benign or malignant tumors was significantly increased (0/44, 0/49, 1/48, 5/47 [$p = 0.033$]).

In Fischer 344 rats, male and female rats were exposed to propachlor in feed for 24 months. A carcinoma of the glandular stomach was observed in one high-dose male rat. No stomach tumors were observed in 250 male and 250 female historical control rats from the testing facility. Stomach tumors are rare in rats, and the U.S. EPA (1997b) attributed this tumor to propachlor treatment. Stomach tumors were also seen in rats treated with structural analogs alachlor and butachlor although the tumor type observed after propachlor treatment was unlike the gastric tumors produced by the above analogs.

Propachlor was administered in feed to CD-1 mice for 18 months. In male mice, there were statistically significant increases in the incidences of hepatocellular adenomas (2/49, 3/50, 2/50, 4/48, and 29/40 for control, low-, mid-low-, mid-high- and high-dose [$p<0.01$] groups, respectively) and combined hepatocellular adenomas or carcinomas (2/49, 3/50, 2/50, 5/48, 31/49 [$p < 0.01$]). The incidence of hepatocellular carcinoma (0/49, 0/50, 0/50, 1/48, 4/49 [$p = 0.059$]) also occurred with a significant positive trend ($p = 0.002$). No treatment related effects were seen in female mice.

U.S. EPA (1997b) noted that propachlor showed *in vitro* clastogenic activity consistent with that of structural analogs alachlor, acetochlor, and dimethenamid. Alachlor and acetochlor are both classified as B2 carcinogens by U.S. EPA and listed under

Proposition 65 as known to cause cancer. U.S. EPA (1997b) also noted that administration of propachlor in rats resulted in tumors at the same sites (stomach and thyroid) as were observed with acetochlor (thyroid), alachlor (stomach/thyroid) and butachlor (stomach/thyroid). In mice, the hepatocellular tumors observed after propachlor treatment were also seen after administration of acetochlor.

Strong inorganic acid mists containing sulfuric acid [CAS No. 7664-93-0 (Sulfuric Acid)]

Evidence of a causal relationship between strong inorganic mists containing sulfuric acid and cancer.

The NTP has listed strong inorganic acid mists containing sulfuric acid as known to be a human carcinogen in the NTP's *Ninth Report on Carcinogens* (NTP, 2000d). The identification was based on sufficient evidence of carcinogenicity from studies in humans that indicate a causal relationship between exposure to strong inorganic acid mists containing sulfuric acid and human cancer. The *Ninth Report on Carcinogens* cites IARC's classification of occupational exposure to strong inorganic acid mists containing sulfuric acid in Group 1 (carcinogenic to humans) [IARC, 1992].

Occupational exposures to strong inorganic acid mists containing sulfuric acid have been associated with laryngeal and lung cancer in humans. The studies cited by NTP (2000d) are as follows: Steenland *et al.* (1988) reported excesses in laryngeal cancer in studies of male workers in pickling operations in the steel industry [standardized incidence ratio (SIR) for laryngeal cancer was 2.30 (95% confidence interval [CI], 1.05-4.36]. In a ten-year follow-up, Steenland (1997) reported a laryngeal cancer rate ratio of 2.2 (95% CI, 1.2-3.7), consistent with previous findings. In a nested case-control study of workers in a U.S. petrochemical plant, Soskolne *et al.* (1984) reported a dose-response for laryngeal cancer risk among workers exposed to moderate (odds ratio of 4.6; 95% CI, 0.83-25.35) or high levels (odds ratio of 13.4; 95% CI, 2.08-85.99) of sulfuric acid. In a Canadian population based case-control study, Soskolne *et al.* (1992) observed a dose-response for laryngeal cancer risk in workers exposed to sulfuric acid mist, with an odds ratio of 2.52 (95% CI, 0.80-7.91) at the lowest levels of exposure and 6.87 (95% CI, 1.00-47.06) at the highest. A population based case-control study in Canada by Siemiatycki (1991) suggested an increase in risk for oat-cell carcinoma of the lung (relative risk of 2.0; 90% CI, 1.3-2.9). Steenland and Beaumont (1989), reporting on the same cohort of workers described by Steenland *et al.* (1988), found an excess of lung cancer in these workers [standardized mortality ratio (SMR) for lung cancer was 1.36 (95% CI, 0.97-1.840)].

NTP (2000d) noted that no adequate experimental animal carcinogenicity studies of sulfuric acid or strong inorganic acid mists containing sulfuric acid have been reported in the literature.

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