EVIDENCE ON THE DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF

Propachlor

DRAFT

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Reproductive and Cancer Hazard Assessment Section
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PREFACE

The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code 25249.5 *et seq.*) requires that the Governor cause to be published a list of those chemicals "known to the state" to cause cancer or reproductive toxicity. The Act specifies that one of the mechanisms by which "a chemical is known to the state to cause cancer or reproductive toxicity [is] if in the opinion of the state's qualified experts the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity" (Health and Safety Code Section 25249.8(b)). The "state's qualified experts" regarding findings of reproductive toxicity are identified as members of the Developmental and Reproductive Toxicant (DART) Identification Committee of the Office of Environmental Health Hazard Assessment's Science Advisory Board (Title 22, California Code of Regulations, Section 12301 (22 CCR 12301)). The lead agency for implementing Proposition 65 is the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency.

Another of the mechanisms by which a chemical may be put on the Proposition 65 list is if the chemical has been formally identified as causing cancer or reproductive toxicity by an organization that has been designated by the State's qualified experts as "authoritative" for purposes of Proposition 65. One such "authoritative body" is the U.S. Environmental Protection Agency (EPA) (22 CCR 12306).

As part of the addition of propachlor to the Toxic Release Inventory (TRI) list (section 313 of the Emergency Planning and Community Right to know Act of 1986), the U.S. EPA stated that there was "sufficient evidence for listing propachlor… based on the available developmental toxicity data" (U.S. EPA 1994a, 1994b). Based upon the TRI listing, OEHHA began the process of adding propachlor to the Proposition 65 list with a Request for Relevant Information (OEHHA 1998a) and a Notice Of Intent to List (OEHHA 1998b). Subsequent evaluation of comments received and supporting data indicated that the necessary criteria for listing propachlor via this mechanism had not been met (22 CCR 12306). As a result, propachlor is being referred to the DART Identification Committee (OEHHA 1999).

This draft Hazard Identification Document provides the DART Identification Committee with information relevant to the reproductive toxicity of propachlor. It should be noted that substantially more data are reviewed in this document than were reviewed for the TRI process.

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A. Abstract

Propachlor (CAS No. 1918-16-7) is an acetanilide herbicide. It is used for pre- and post-emergence control of many grasses and some broadleaf weeds. It is not registered or used in California. It is possible that people living in California could be exposed to propachlor due to importation of propachlor-treated crops from other areas.

Propachlor appears to undergo rapid absorption, distribution, metabolism, and excretion with little tissue retention. The metabolism is complex, with multiple conjugation and cleavage reactions, some involving intestinal microflora and enterohepatic recirculation. Eleven metabolites have been identified. Excretion is mainly in urine.

Propachlor has relatively low acute toxicity by the oral, inhalation, and dermal routes. Propachlor was found to be a severe eye irritant in rabbits. In some studies where propachlor was administered in feed, palatability was considered to be a problem at higher concentrations. Reduced food consumption, body weight or weight gain, increased liver weight and hypertrophy, reduced kidney weight, and stomach lesions were common observations in propachlor-treated animals.

No studies in humans of the potential developmental or reproductive toxicity of propachlor were located. Several relevant studies are available in rabbits, rats, mice, and dogs.

In a rabbit developmental toxicity study, higher pre- and post-implantation losses, lower litter sizes, and increased malformations were observed in the middle and high dose groups compared to controls. No adverse maternal effects were observed. However, some of the developmental effects were not statistically significant, and the magnitude of the effects was greatest in the middle dose group, i.e. there was not a clear dose-response relationship. A later pair of developmental studies used the same strain of rabbits and higher doses. In the range-finding study, high levels of maternal mortality were observed in the three highest dose groups. No adverse developmental effects were observed in the fetuses of surviving rabbits. In the main study, in the high dose group, severely reduced maternal food consumption compared to controls was observed (statistically significant). Maternal animals in the high dose group lost weight during treatment, while the control group gained weight (statistically significant difference). In the high dose group, early and late resorptions were higher, live litter size was lower, and fetal weight was lower than controls (none statistically significant). No increase in malformations was observed. In the high dose group, an increase in a variation, bent hyoid arch, was observed (statistically significant on a litter, but not fetal, basis).

In a rat developmental toxicity study (published in Bulgarian, partially translated by OEHHA staff), rats were treated with Ramrod, a commercial preparation of propachlor (stated to be 65% propachlor). In this study, increased pre-implantation losses and fetal anomalies were observed. This study is difficult to evaluate, due to poorly defined test substance and doses, lack of data on maternal effects, and incomplete data on developmental effects. A later pair of rat developmental studies were conducted for pesticide registration purposes with relatively pure propachlor. In the range-finding study, all maternal animals in the three highest dose groups died. In the two remaining dose groups, lower maternal body weight and weight gain was

observed (no statistical tests were reported). Higher pre-implantation loss, lower total implantations, and lower live litter size were also observed in the two remaining dose groups compared to controls (no statistical tests). The main study covered the same dose range as the two groups with survivors in the range-finding study, while using three doses and larger numbers of animals. No adverse maternal or developmental effects were observed.

In a rat reproductive toxicity study, propachlor was administered to male and female rats in food for two generations. In the second (F1) generation, adult male food consumption and body weights were reduced in the high concentration group compared to controls (sometimes statistically significant). Adult female food consumption and body weights were generally similar among groups. Sporadic reductions in fertility were observed, but these were not dose-related. No adverse developmental effects (litter size, pup weight) were observed. A later rat two-generation reproductive study used much higher concentrations. Reduced maternal and paternal food consumption and body weight were observed in the high concentration (usually statistically significant) and the middle concentration (occasionally statistically significant) groups compared to controls. No adverse effects on fertility or other reproductive indices were observed. Reduced live litter size and pup weight at birth were observed in the high concentration group (statistically significant). Reduced pup survival and growth during lactation were also observed in this group (statistically significant). The effects were sufficiently severe that this group was discontinued after the first generation. Lower pup birth weight was also observed in the middle concentration groups for both generations (not statistically significant).

A study in a milk goat found very little transfer of propachlor to milk. Extrapolation of this observation to rats is problematic, due to much higher doses in the rat studies and possible differences in metabolism.

In a male dominant lethal study, male rats were treated with propachlor in food for 10 weeks plus two rounds of co-housing with untreated females. Reduced male food consumption, body weight, and body weight gain were observed in the propachlor high and middle concentration groups compared to controls (statistically significant). There were no effects of propachlor on male fertility, females becoming pregnant, total implantations, live implantations, or resorptions (i.e. no dominant lethal effects).

Numerous studies have examined the effects of propachlor on weight and/or gross and microscopic pathology of ovaries and sometimes other female reproductive organs. These include the two rat reproductive studies, and subchronic and chronic studies in mice, rats, and dogs. No adverse effects were observed.

Numerous studies have examined the effects of propachlor on weight and/or gross and microscopic pathology of testes and sometimes other male reproductive organs. These include the two rat reproductive studies, the male rat dominant lethal study, and subchronic and chronic studies in mice, rats, and dogs. In one subchronic study (published in Bulgarian, partially translated by OEHHA staff), rats were treated with Ramrod. In this study, microscopic observations found disrupted spermatogenesis, including effects on spermatogonia and maturation. This study is difficult to evaluate, due to poorly defined test substance, incomplete reporting of male reproductive effects, and lack of data on systemic effects. In numerous other

studies of mice, rats or dogs treated with relatively pure propachlor, gross and/or microscopic observations found no adverse effects on testes or other male reproductive organs.

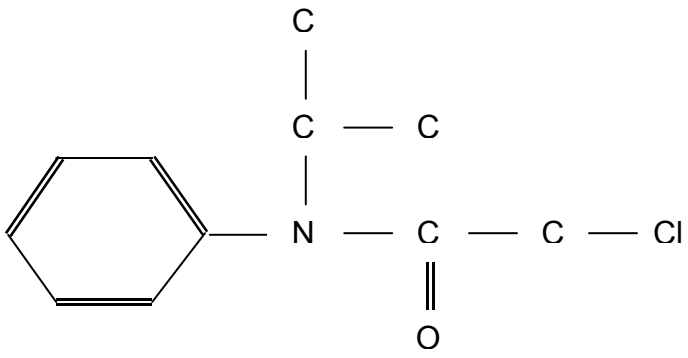
In some studies, increases or decreases in absolute testes weight were observed (a few statistically significant). In several studies, relative testes weights were increased, in part due to reduced body weights (sometimes statistically significant). Reduced absolute testes weights (statistically significant) were observed in one subchronic study each in mice and rats at very high concentrations of propachlor. Reduced body weights (statistically significant) were also observed at these concentrations. Relative testes weights were not affected in the mouse study, and were increased in the rat study (statistically significant). Gross and microscopic examination of the testes found no propachlor treatment related effects in these studies. Increased absolute and relative testes weights (statistically significant) were observed in a chronic rat study at the high concentration at the terminal sacrifice but not the interim sacrifice. Also at the terminal sacrifice, almost all males in the control and propachlor treated groups had interstitial cell tumors, aspermia, and bilateral atrophy of the seminiferous tubules.

B. Introduction

B.1. Chemical structure and main physical characteristics

Propachlor (CAS No. 1918-16-7) is an acetanilide herbicide. A systematic name is 2-chloro-N-isopropylacetanilide. It has a molecular mass of 211.7 D. It is a light tan solid at room temperature. It is slightly soluble in water, and soluble in common organic solvents except aliphatic hydrocarbons (Budavari 1989, Meister 2001, U.S. EPA 1998, WHO 1993). The structure is shown in Figure 1.

Figure 1. Structure of Propachlor



B.2. California use and exposure information

Propachlor is not registered for use in California (CDPR 2003). No reports of recent propachlor use in California have been found (CDPR 2000a, 2000b, 2001, 2002).

Propachlor is a pre-emergence and early post-emergence herbicide used for control of many grasses and some broadleaf weeds (Meister 2001, U.S. EPA 1998, WHO 1993). It was first registered for use in the United States (U.S.) in 1964. It was found eligible for reregistration by the U.S. EPA in 1998. Average annual use in the U.S. from 1987 to 1996 was estimated as 2.1 million pounds. The main crops were sorghum (75% of total usage), field corn, and bulb crops (garlic, leeks, and onions) (U.S.EPA 1998). Several other crops may have been treated previously or may be treated currently with propachlor in other countries (HSDB 2003, WHO 1993). Exposure of people living in California could result from importation of propachlor-treated crops from other states or countries.

B.3. Pharmacokinetics

The pharmacokinetics of propachlor have been reviewed (U.S. EPA 1998, WHO 1993). Propachlor is readily absorbed orally. The metabolism is complex, with multiple conjugation and cleavage reactions, some involving intestinal microflora. Most propachlor and its metabolites are excreted in the urine. The following summary is from the U.S. EPA Reregistration Eligibility Decision (RED) for propachlor (U.S. EPA 1998):

"In a metabolism study in rats in which single doses of 25 mg propachlor/kg of body weight were administered orally, 91% of the dose was recovered in 56 hours, with 68% of the dose being excreted in urine, 10% in the feces, and 4% was found in the carcass. Eleven metabolites were identified. The metabolic fate of propachlor depends to a large extent on the presence of the intestinal microflora. Propachlor metabolites can make 3 or more cycles in the enterohepatic circulation. In the first cycle, propachlor is metabolized via the mercapturic acid pathway and the conjugates are excreted in bile. The second cycle is initiated when the biliary mercapturic acid pathway metabolites are metabolized by a microflora C-S lyase to reabsorbable metabolites, which are then metabolized to glucuronides that are secreted with the bile. Subsequent cycles result from microfloral B-glucuronidase activity. Propachlor appears to undergo rapid absorption, distribution, metabolism, and excretion with little, if any, tissue retention in rats. From the studies available… it can be stated that, following initial glutathione conjugation, metabolism proceeds primarily via the mercapturic acid pathway with concurrent oxidative reactions and glucuronic acid conjugation. Initially-formed metabolites undergo extensive excretion and enterohepatic circulation."

No information on the distribution of propachlor or its metabolites to the placenta or fetus was located by OEHHA staff. Transfer of propachlor to milk was observed in a milk goat. The amount and concentration in milk appeared to be very small compared to the equivalent amount and concentration in food (see Section C.3.2).

B.4. Non-developmental and reproductive toxicities.

The toxicities of propachlor have recently been reviewed, based upon a completed pesticide registration studies database (U.S. EPA 1998). The following summaries are based upon this review. Additional information on the subchronic and chronic studies is summarized in Sections D.2 and E.2.

Propachlor has a relatively low acute toxicity by oral, dermal, and inhalation routes. In rats, the acute oral LD_{50} was found to be 1.8 g/kg. In rabbits, the dermal LD_{50} was greater than 20 g/kg. In rats, the inhalation LC_{50} was equal to or greater than 1.2 mg/L.

Propachlor was found to be a severe eye irritant (highest toxicity category) when administered to rabbits in the primary eye irritation test. It was found to be a slight dermal irritant by the dermal route in rabbits, but a strong dermal sensitizer in guinea pigs.

In subchronic and chronic studies with propachlor administered in feed, palatability was found to be a problem. Reduced food consumption and reduced weight gain were observed in subchronic studies in rats, mice, and dogs treated with propachlor in feed at high concentrations. Other possible effects were difficult to interpret due to the severity of the food consumption and weight effects in the high concentration groups.

In some chronic studies, animals were started at a moderate concentration and then the concentration was increased gradually to the final high concentration. A combined chronic toxicity/carcinogenicity study in rats used treatment in feed at 0, 100, 300, 1,000 and 2,500/5,000 ppm (females/males) for two years. The high concentration groups were started at 1,000 ppm and ramped up to the final concentrations. Reduced body weight compared to controls was observed in the two highest concentration groups. Increased liver and decreased kidney weight were observed in males and females in the high concentration group. Stomach lesions were observed in males at the high concentration and females at the two highest concentrations. The incidence and severity of hepatocellular hypertrophy were increased in a concentration-related manner in both sexes. Reduced thyroid weight was observed in females at the high concentration. Another chronic study in rats did not use concentrations high enough to elicit indications of toxicity (maximum 500 ppm).

A chronic study in dogs used treatment in feed at 0, 25, 250, or 1,000 ppm for one year. Most groups treated with propachlor displayed reduced food consumption. Reduced body weight was observed in males at the middle and high concentrations and in females at the high concentration. No other indications of toxicity were observed.

A carcinogenicity study in mice used treatment in feed at 0, 100, 500, 1,500, or 6,000 ppm for 18 months. The high concentration groups were started at 1,500 ppm and ramped up to the final concentration. Reduced food consumption, body weight, and body weight gains were observed in males at the two highest concentrations, and in females at the highest concentration. Concentration-related increases in liver weights were observed in both sexes. Reduced kidney weights were observed in both sexes at the high concentration. Liver and stomach lesions were observed in males at the two highest concentration levels, and in females at the high concentration level. Another chronic study in mice did not use concentrations high enough to elicit indications of toxicity (maximum 500 ppm).

An acute neurotoxicity study in rats used treatment at 0, 175, 350, or 700 mg/kg by gavage. At 700 mg/kg, deaths occurred in both sexes. Increased landing foot splay was observed 7 hours after treatment in females at the middle and high doses. A subchronic neurotoxicity study in rats used treatment in feed at 0, 100, 1,000 or 2,500 ppm. Reduced food consumption, body weight, and body weight gain was observed in both sexes at the high concentration. None of the neurotoxicity parameters examined were affected by propachlor treatment in either sex.

In summary, animal studies indicate that propachlor is highly toxic when administered directly to the eye. Treatment by oral routes indicates relatively low systemic toxicity. Palatability appears to be a problem when animals are treated at high concentrations in feed. Reduced food consumption, body weight, and body weight gains were frequently observed. Typical systemic effects in chronic studies included increased liver weight and liver lesions, reduced kidney

controls at 3.0 and 30 mg/kg/d (statistically significant). In the F0/F1 mating, fertility was reduced at 3.0 mg/kg/d compared to controls (statistically significant), but was similar to controls at 30 mg/kg/d. In the F1/F2a mating, fertility was reduced at 3.0 mg/kg/d compared to controls (statistically significant) and lower than controls at 30 mg/kg/d (not statistically significant). In the F1/F2b mating, fertility was similar among groups. Live litter size on pnd 1 for all three litters was similar among groups. See Table 28. Gross and microscopic examination of F0 and F1 testes and other male reproductive organs found no propachlor treatment related lesions.

Table 27. Selected male data from rat reproductive study (Groya 1986). [1]

Group (mg/kg/d)		0	0.3	3.0	30
F0 males in study		29 [2]	30	30	30
F0 male food consumption (g/animal/ day)	Days 1-7	16.3 ± 0.9	16.4 ± 1.0	16.6 ± 0.9	16.4 ± 0.6
	Days 99-104 [3]	17.8 ± 1.5	18.3 ± 1.1	18.4 ± 1.2	17.8 ± 1.3
F0 male body weight (g)	Day 0	131 ± 9	129 ± 8	127 ± 8	126 ± 6*
	Day 105 [3]	350 ± 19	356 ± 18	355 ± 17	342 ± 20
	At sacrifice	344 ± 20	338 ± 18	351 ± 14	338 ± 20
F0 male liver weight	Absolute (g)	9.03 ± 0.70	8.79 ± 0.50	9.31 ± 0.46	9.57 ± 0.81
	Relative (g/100 g bw)	2.62 ± 0.09	2.60 ± 0.13	2.66 ± 0.10	2.83 ± 0.13*
F1 males in study		30	30	30	30
F1 male food consumption (g/animal/ day)	Days 2-7	15.5 ± 1.0	15.4 ± 0.8	15.1 ± 1.0	14.8 ± 1.1*
	Days 113-119 [3]	17.7 ± 1.6	17.8 ± 1.2	18.0 ± 1.0	16.9 ± 1.2
F1 male body weight (g)	Day 0	130 ± 13	132 ± 11	132 ± 12	124 ± 15
	Day 118 [3]	341 ± 21	337 ± 17	337 ± 20	325 ± 16*
	Day 258	394 ± 26	382 ± 21	387 ± 31	369 ± 23*
	At sacrifice	371 ± 25	358 ± 20	362 ± 30	345 ± 23*
F1 male liver weight	Absolute (g)	9.70 ± 0.86	9.41 ± 0.78	9.87 ± 0.95	9.76 ± 0.86
	Relative (g/100 g bw)	2.63 ± 0.10	2.62 ± 0.13	2.73 ± 0.10*	2.83 ± 0.12*

(1) Data are numbers or averages ± SD.
(2) "Animal discovered to be a female, and removed from the study."
(3) Start of mating.
* $P < 0.05$ statistically significant difference compared to controls, Dunnett's test.

Table 28. Selected data from rat reproductive study (Groya 1986). [1]

Group (mg/kg/d)		0	0.3	3.0	30
F0 male testes weight	Absolute (g)	3.12 ± 0.12	3.09 ± 0.12	3.11 ± 0.12	3.08 ± 0.19
	Relative (g/100 g bw)	0.91 ± 0.08	0.92 ± 0.05	0.89 ± 0.04	0.91 ± 0.07
F0/F1 fertility [number of females delivering a litter/number mated (%)]		28/30 (93%)	24/30 (80%)	21[(2)]/30[#] (70%)	26/30 (87%)
F0/F1 live litter size pnd 1		8.8 ± 3.91	9.7 ± 1.90	10.0 ± 2.35	9.0 ± 2.99
F1 male testes weight	Absolute (g)	3.10 ± 0.49	3.25 ± 0.08	3.38 ± 0.16	3.26 ± 0.24
	Relative (g/100 g bw)	0.85 ± 0.13	0.91 ± 0.06	0.92 ± 0.07*	0.95 ± 0.08*
F1/F2a fertility [number of females delivering a litter/number mated (%)]		25/30 (83%)	26/30 (87%)	18/30[#] (60%)	19/30 (63%)
F1/F2a live litter size pnd 1		8.2 ± 3.04	8.7 ± 2.54	8.0 ± 2.79	7.0 ± 3.55
F1/F2b fertility [number of females delivering a litter/number mated (%)]		25/30 (83%)	25/30 (83%)	25/30 (83%)	24/30 (80%)
F1/F2b live litter size pnd 1		10.0 ± 3.51	11.2 ± 3.00	9.3 ± 4.05	9.8 ± 3.92

(1) Data are numbers, percentages, or averages ± SD.
(2) Includes one female that died during gestation with 10 fetuses.
* $P < 0.05$ statistically significant difference compared to controls, Dunnett's test.
[#] $P < 0.05$ statistically significant difference from controls, Fisher Exact Test.

Lemen and Thake 1995

This study was partially described in the developmental and female reproductive sections (sections C.2.2 and D.1). Data relevant to possible male reproductive toxicity are summarized in this section. Male and female Sprague-Dawley rats were treated with propachlor (97.83% purity) in a two generation reproduction study with one litter in each generation. Animals were treated in food at concentrations of 0, 100, 1,000, or 2,500 (males) or 5,000 (females) ppm. For the high concentration male group, the initial concentration was 1,000 ppm, which was ramped up by 500 ppm per week to the final concentration on week five. These concentrations corresponded to average doses of 0, 6.9, 67, and 166 mg/kg/d for the F0 males and 0, 7.2, and 72 mg/kg/d for the F1 males. Due to severe adverse effects in the high concentration group, this group was discontinued after the first litter. There were 30 animals/sex/group. F0 and F1 adult animals were treated for at least 10 weeks before mating, and during mating, gestation, and lactation. Matings were one male to one female, unless no evidence of copulation was observed, in which case the female was mated to a second, proven, male. Litters with more than 8 pups were culled to 8 pups on pnd 4. Parental body weight, food consumption, clinical signs, and gross and histopathology were reported. Fertility, gestation length, litter size, pup weights, pup survival, and pup gross and histopathology were reported.

One F0 male in the 2,500 ppm group was sacrificed in extremis. No cause of morbidity was reported; the author considered the morbidity to be incidental to treatment. All other F0 males survived until scheduled sacrifice. F0 males had reduced food consumption in the 2,500 ppm group compared to controls throughout the study (statistically significant). F0 males had reduced food consumption in the 1,000 ppm group compared to controls (statistically significant for the first week, sporadically statistically significant thereafter). Males in the 2,500 ppm group had reduced body weight compared to controls from about the third week of treatment onwards (statistically significant). By the end of the premating treatment period, male body weight in the 2,500 ppm group was about 85% of controls. Males in the 1,000 ppm group had lower body weight than controls from about the third week of treatment onwards (sporadically statistically significant). By the end of the premating treatment period, male body weight in the 1,000 ppm group was about 94% of controls. Absolute liver weights were similar among the 0, 100, and 1,000 ppm groups (no data were reported for the 2,500 ppm group). Relative liver weight was increased in the 1,000 ppm group compared to controls (statistically significant) (no data were reported for the 2,500 ppm group). See Table 29. Increased incidence of centrilobular/midzonal hepatocellular hypertrophy was observed in the 1,000 ppm group compared to controls (13/30 vs. 0/30, statistically significant). No data for the 2,500 ppm group on gross or microscopic organ pathology were reported.

As noted above, the high concentration (2,500 ppm in males) group was discontinued after the first litter, so there are no data for the F1 adult males. One F1 adult male in the 1,000 ppm group was found dead. No cause of death was reported; the author considered the death to be incidental to treatment. All other F1 adult males survived until scheduled sacrifice. F1 males had reduced food consumption in the 1,000 ppm group compared to controls throughout the study (statistically significant). F1 males had slightly lower food consumption in the 100 ppm group than controls (not usually statistically significant). F1 males had reduced body weight in the 1,000 ppm group compared to controls from the beginning of treatment, which continued

throughout the treatment period (statistically significant). By the end of the premating treatment period, the 1,000 ppm group male body weight was about 89% of controls. Males had slightly lower body weight in the 100 ppm group than controls throughout the treatment period (not statistically significant). By the end of the premating treatment period, the 100 ppm group male body weight was about 96% of controls. Absolute liver weights were similar among groups. Relative liver weight was increased in the 1,000 ppm group compared to controls (statistically significant). See Table 30. Increased incidence of centrilobular/midzonal hepatocellular hypertrophy was observed in the 1,000 ppm group compared to controls (16/30 vs. 0/30, statistically significant).

In the F0/F1 mating, precoital length, and percentages of males with confirmed copulation, males impregnating females, and females pregnant were similar among groups. Live litter size was reduced in the 2,500 ppm (males) group compared to controls (statistically significant). F0 male absolute testes weights were slightly higher in the 100 and 1,000 ppm groups compared to controls (not statistically significant). Relative testes weights were increased in the 100 and 1,000 ppm groups compared to controls (statistically significant). No testes weight data for the 2,500 ppm group were reported. See Table 31. Gross and microscopic examination of F0 testes found no propachlor treatment related lesions.

In the F1/F2 mating, the success of the control group was low compared to the F0/F1 control group. In the F1/F2 mating, precoital length was reduced in the 100 and 1,000 ppm groups compared to controls (statistically significant). The percentages of males with confirmed copulation, males impregnating females, and females pregnant were increased in the 100 and 1,000 ppm groups compared to controls (statistically significant). Live litter size was similar among groups. F1 male absolute testes weights were similar among groups. Relative testes weight was increased in the 1,000 ppm group compared to controls (statistically significant). See Table 32. Gross and microscopic examination of F1 testes found no propachlor treatment related lesions.

Table 29. Selected male data from rat reproductive study (Lemen and Thake 1995). [1]

Group (ppm)		0	100	1,000	2,500
F0 males in study		30	30	30	30
F0 male food consumption (g/animal/ day)	Days 1-8	29.4 ± 2.25	29.2 ± 2.58	25.8 ± 2.53**	26.1 ± 1.95**
	Days 14-21	31.2 ± 2.78	30.8 ± 2.02	30.3 ± 2.44	26.5 ± 2.61**
	Days 63-70 [2]	31.4 ± 2.37	30.0 ± 2.54	30.0 ± 2.61	27.1 ± 2.32**
F0 male body weight (g)	Pre-test	296.8 ± 31.67	296.8 ± 31.53	296.6 ± 31.74	296.6 ± 31.08
	Day 21	423.1 ± 37.56	412.0 ± 41.04	406.9 ± 40.05	386.4 ± 39.06**
	Day 70 [2]	568.7 ± 52.21	539.9 ± 57.66	533.7 ± 60.49*	483.5 ± 51.75**
	Day 105	627.8 ± 59.00	601.8 ± 64.00	590.1 ± 74.59	526.6 ± 57.76**
	Day 142	668.0 ± 68.71	644.3 ± 70.48	623.5 ± 83.25*	548.4 ± 61.77**
F0 male liver weight	Absolute (g)	19.1 ± 2.71	18.8 ± 2.55	19.8 ± 3.01	ND
	Relative (% of bw)	2.96 ± 0.225	3.03 ± 0.207	3.31 ± 0.264**	ND

(1) Data are numbers, percentages, or averages ± SD.
(2) Start of mating.
ND = No Data reported for that group.
* $P < 0.05$ statistically significant difference from controls, Dunnett's Test.
** $P < 0.01$ statistically significant difference from controls, Dunnett's Test.

Table 30. Selected male data from rat reproductive study (Lemen and Thake 1995). [1]

Group (ppm)		0	100	1,000
F1 males in study		30	30	30
F1 male food consumption (g/animal/ day)	Days 1-9	20.2 ± 2.75	20.1 ± 2.69	18.2 ± 1.90**
	Days 14-21	30.1 ± 3.42	29.6 ± 3.04	26.9 ± 2.58**
	Days 70-77 [2]	29.6 ± 3.32	28.7 ± 2.58*	27.5 ± 2.51*
F1 male body weight (g)	Day 1	185.0 ± 32.86	179.8 ± 34.64	162.1 ± 17.53**
	Day 21	367.9 ± 47.31	354.2 ± 45.08	327.2 ± 29.78**
	Day 77 [2]	590.6 ± 54.77	565.3 ± 63.98	524.1 ± 45.93**
	D 141	672.1 ± 62.92	645.1 ± 83.00	600.8 ± 60.93**
F1 male liver weight	Absolute (g)	19.6 ± 2.93	18.9 ± 2.84	19.3 ± 2.77
	Relative (% of bw)	3.01 ± 0.291	3.06 ± 0.219	3.37 ± 0.297**

(1) Data are numbers or averages ± SD.
(2) Start of mating.
* $P < 0.05$ statistically significant difference from controls, Dunnett's Test.
** $P < 0.01$ statistically significant difference from controls, Dunnett's Test.

Table 31. Selected data from rat reproductive study (Lemen and Thake 1995). (1)

Group (ppm)		0	100	1,000	2,500
F0 testes weight	Absolute (g)	3.67 ± 0.260	3.82 ± 0.394	3.82 ± 0.316	ND
	Relative (% of bw)	0.58 ± 0.059	0.62 ± 0.065*	0.65 ± 0.082**	ND
F0 females mated		30	30	30	30
Precoital length (days)		3.1 ± 3.6	3.1 ± 3.4	2.7 ± 1.6	3.2 ± 2.7
F0 males with confirmed copulation/total paired (%)		93.3%	93.3%	100%	93.3%
F0 males impregnating females/total paired (%)		86.7%	90.0%	86.7%	80.0%
F0 females pregnant/total paired (%)		93.3%	96.7%	86.7%	86.7%
F0/F1 live litter size at birth		14.0 ± 3.60	14.4 ± 2.31	14.9 ± 2.29	12.5 ± 3.71#
F0/F1 dead pups/litter at birth		0.10 ± 0.315	0.34 ± 0.769	0.62 ± 2.76	0.73 ± 2.55

(1) Data are numbers, percentages, or averages ± SD.
ND = No Data reported for that group.
# P < 0.05 statistically significant difference compared to controls, Mann-Whitney

Table 32. Selected data from rat reproductive study (Lemen and Thake 1995). (1)

Group (ppm)		0	100	1,000
F1 testes weight	Absolute (g)	3.89 ± 0.270	3.84 ± 0.312	3.97 ± 0.300
	Relative (% of bw)	0.60 ± 0.062	0.62 ± 0.066	0.70 ± 0.074**
F1 females mated		30	30	30
Precoital length (days)		6.6 ± 5.5	2.8 ± 2.0#	3.1 ± 2.3#
F1 males with confirmed copulation/total paired (%)		76.7%	100%@@	96.7%@
F1 males impregnating females/total paired (%)		56.7%	86.7%@@	93.3%@@
F1 females pregnant/total paired (%)		60.0%	86.7%@	93.3%@@
F1/F2 live litter size at birth		12.7 ± 3.48	12.7 ± 2.55	12.8 ± 3.16
F1/F2 dead pups/litter at birth		0.06 ± 0.236	0.08 ± 0.271	0.0 ± 0.0

(1) Data are numbers, percentages, or averages ± SD.
# P < 0.05 statistically significant difference compared to controls, Mann-Whitney.
@ P < 0.05 statistically significant difference compared to controls, chi-square.
@@ P < 0.01 statistically significant difference compared to controls, chi-square.

Naylor 1994

In this dominant lethal study, male Sprague-Dawley rats were treated with propachlor in food at 0, 300, 1,000, or 2,500 ppm for approximately 10 weeks plus two rounds of mating. The doses during the pre-mating phase were 0, 13.6, 43.9 or 111.8 mg/kg/d, respectively. Males in the 2,500 group were started at 1,000 ppm, and then ramped up to 2,500 ppm. Additionally, a positive control group was treated with 0.3 mg/kg triethylenemelamine (TEM) once by intraperitoneal injection 3 days prior to mating. There were 35 males/group. Males were co-housed with one untreated female each for 5 days, followed by two days rest, and then co-housed with a second untreated female for 5 days. It was not clear from the report how or if the females were prevented from being exposed to the male's food containing propachlor. Males were sacrificed after the second mating period. Females were sacrificed approximately 14 days after confirmation of copulation. Females without confirmed copulation were sacrificed 12-16 days after the last night of co-housing. Male food consumption, body weight, and body weight gain were reported. Male fertility, females becoming pregnant, total and viable implantations/female, resorptions/female, and gross pathology of selected male organs were reported.

One male in the 1,000 ppm group died during the study. All other males survived until scheduled sacrifice. Food consumption, body weights, and body weight gains were reduced in the 1,000 and 2,500 ppm propachlor groups compared to negative controls (statistically significant). The positive control (TEM) group was similar to negative controls for these parameters. See Table 33.

Male fertility, percentage of females pregnant, total implantations/female, live implantations/female, and resorptions/female were similar in all propachlor treated groups to negative controls. The positive control (TEM) group had lower male fertility (not statistically significant), reduced percentage of females pregnant (statistically significant), reduced total and viable implants/female (statistically significant), and increased resorptions/female (statistically significant) compared to negative controls. Gross examination of the testes and other male reproductive organs found no effects attributable to propachlor treatment. See Table 34.

Table 33. Selected male data from rat male dominant lethal study (Naylor 1994). [1]

Group		Propachlor (ppm)				TEM [2] 0.3 mg/kg
		0	300	1,000	2,500	
No. males in study		35	35	35	35	35
No. males died		0	0	1	0	0
Male food consumption (g/animal/ day)	Days 1-9	29.2 ± 2.24	ND	ND	23.4 ± 3.62**	ND
	Days 22-29	30.4 ± 2.26	30.0 ± 2.98	25.6 ± 2.79**	24.3 ± 1.97**	30.3 ± 2.63
	Days 81-88 [3]	29.4 ± 2.71	28.9 ± 3.04	27.3 ± 2.23*	25.3 ± 1.92**	28.9 ± 4.17
Male body weight (g)	Pre-test	502.9 ± 30.37	503.2 ± 32.22	502.9 ± 31.84	502.8 ± 29.92	502.7 ± 30.86
	Day 22	570.9 ± 37.39	574.8 ± 41.63	570.9 ± 43.38	531.8 ± 32.21**	572.3 ± 44.92
	Day 88 [3]	701.3 ± 60.03	694.2 ± 67.28	660.0 ± 60.39*	604.5 ± 43.70**	698.5 ± 65.55
	Day 103	688.1 ± 58.21	688.0 ± 66.77	649.1 ± 59.85*	591.8 ± 42.16**	679.1 ± 68.32
Male body weight gain (g)	Days 22-88	130.4 ± 28.70	119.4 ± 32.95	89.4 ± 25.04**	72.6 ± 16.70**	126.2 ± 28.98

(1) Data are numbers, percentages, or averages ± SD.
(2) TEM = Triethylenemelamine, positive control group.
(3) Start of mating.
ND = No Data reported for that group.
* $P < 0.05$ statistically significant difference from controls, Dunnett's Test.
** $P < 0.01$ statistically significant difference from controls, Dunnett's Test.

Table 34. Selected data from rat male dominant lethal study (Naylor 1994). [1]

Group	Propachlor (ppm)				TEM [2] 0.3 mg/kg
	0	300	1,000	2,500	
No. males fertile/ No. co-housed (%)	32/35 (91.4%)	32/35 (91.4%)	34/34 (100%)	35/35 (100%)	26/35 (74.3%)
No. females pregnant/ No. co-housed (%)	57/70 (81.4%)	55/70 (78.6%)	61/68 (89.7%)	59/70 (84.3%)	42/70## (60.0%)
Total implants/female	16.51 ± 3.31	15.47 ± 4.54	16.70 ± 2.33	16.03 ± 2.71	7.90 ± 4.49@@
Viable implants/female	15.21 ± 3.41	14.36 ± 4.71	15.49 ± 2.45	14.86 ± 3.16	0.43 ± 1.11@@
Resorptions	1.30 ± 1.35	1.11 ± 1.37	1.21 ± 1.01	1.17 ± 1.21	7.48 ± 4.03@@

(1) Data are numbers, percentages, or averages ± SD.
(2) TEM = Triethylenemelamine, positive control group.
$P < 0.01$ statistically significant difference compared to controls, Chi-square (one tailed).
@@ $P < 0.01$ statistically significant difference compared to controls, ANOVA and Freeman-Tukey (one-tailed).

E.2. Subchronic and chronic studies

E.2.1. Studies in mice

Hamada 1987a

Male and female CD-1 mice were treated with propachlor (96.1% purity) in feed at 0, 10, 50, or 500 ppm for up to 18 months. In males, this corresponded to doses of 0, 1.62, 8.12, and 81.25 mg/kg/d. There were initially 60 animals/sex/group. After 12 months, 10 animals/sex/group were sacrificed. Surviving animals were sacrificed after 18 months. Survival, body weight and weight gain, food consumption, selected organ weight, and gross and microscopic pathology were reported.

Male survival, food consumption, and body weight were similar among groups. At terminal sacrifice, organ weights were measured for only 10 males/group. Liver weight varied somewhat between groups, but the differences were not statistically significant and there was no concentration related trend. Testes weights were similar among groups. See Table 35. Gross and microscopic examination found no propachlor treatment related effects.

Table 35. Selected data from mouse chronic study (Hamada 1987a). [1]

Group (ppm)		0	10	50	500
Initial number of males		60	60	60	60
Unscheduled deaths		12	13	13	17
Male food consumption (g/animal/ week)	Week 1	48.6 ± 4.54	47.5 ± 5.18	48.8 ± 6.15	49.1 ± 6.22
	Week 4	45.2 ± 4.82	47.3 ± 5.97	48.2 ± 5.22	47.9 ± 4.69
	Week 13	49.2 ± 6.15	48.0 ± 7.44	45.6 ± 4.93	45.0 ± 4.75
	Week 50	36.4 ± 3.43	36.2 ± 2.88	34.7 ± 4.51	35.5 ± 3.43
	Week 78	39.5 ± 4.16	39.8 ± 3.78	38.5 ± 5.54	39.0 ± 3.21
Male body weight (g)	start	31.0 ± 2.43	30.6 ± 2.37	31.1 ± 2.18	31.5 ± 2.24
	Week 4	35.0 ± 2.41	34.5 ± 2.24	34.2 ± 2.52	34.5 ± 2.67
	Week 13	37.5 ± 2.63	37.2 ± 2.30	37.6 ± 2.79	37.2 ± 2.70
	Week 50	39.2 ± 4.17	40.3 ± 3.98	38.0 ± 5.98	38.6 ± 4.01
	Week 78	38.9 ± 3.08	39.3 ± 3.76	40.1 ± 4.09	39.0 ± 2.98
Number of males for which organ weights were measured at terminal sacrifice		10	10	10	10
Liver and gallbladder weight	Absolute (g)	1.57 ± 0.21	2.10 ± 0.89	1.67 ± 0.68	1.73 ± 0.30
	Relative (%)	4.747 ± 0.611	6.317 ± 0.570	4.032 ± 1.423	5.076 ± 0.991
Testes weight	Absolute (g)	0.36 ± 0.04	0.35 ± 0.06	0.36 ± 0.07	0.37 ± 0.05
	Relative (%)	1.190 ± 0.129	1.059 ± 0.177	1.040 ± 0.172	1.002 ± 0.133

(1) Data are numbers or averages ± SD.
No statistically significant differences were found (ANOVA, Dunnett's).

Naylor and Ruecker 1996

Male and female CD-1 mice were treated with propachlor in diet for up to 18 months. Propachlor target concentrations were 0, 100, 500, 1,500, or 6,000 ppm. In males, these corresponded to doses of 0, 14.6, 75.0, 222.9, or 847.3 mg/kg/d, respectively. Mice in the highest concentration group were started at 1,500 ppm and ramped up by 500 ppm per week to the final concentration of 6,000 ppm at 10 weeks. There were initially 60 animals/sex/group. Ten animals/sex/group were sacrificed after 12 months, and surviving animals were sacrificed after 18 months. Mortality, food consumption, body weight and weight gain, clinical signs, some organ weights, and gross and microscopic pathology were reported.

Survival was similar among groups. Males in the 1,500 and 6,000 ppm groups had reduced food consumption compared to controls (frequently statistically significant). Males in the 6,000 ppm group had reduced body weight compared to controls after about 8 weeks treatment (89% of controls at terminal sacrifice, statistically significant). At the interim and final sacrifices, males in the 500, 1,500, and 6,000 ppm groups had increased absolute and relative liver weight compared to controls (statistically significant). See Table 36. At the interim sacrifice (12 months), males in 1,500 and 6,000 ppm groups had increased incidence of centrilobular/midzonal hepatocellular hypertrophy compared to controls (statistically significant at 6,000 ppm). At the terminal sacrifice, males in the 1,500 and 6,000 ppm groups had increased incidence of centrilobular/midzonal hepatocellular hypertrophy and eosinophilic foci compared to controls (statistically significant).

Testes weights were similar among groups, except the relative testes weight at terminal sacrifice in the 6,000 ppm group was increased compared to controls (statistically significant). See Table 37. Gross and microscopic examination of testes and epididymides found no propachlor related lesions.

Table 36. Selected data from mouse chronic study (Naylor and Ruecker 1996). [1]

Group (ppm)		0	100	500	1,500	6,000
Initial number of males		60	60	60	60	60
Found dead or sacrificed in extremis		5	3	12	7	10
Male food consumption (g/animal/ day)	Days 1-8	5.6 ± 0.82	5.2 ± 0.80*	5.1 ± 0.34**	5.0 ± 0.74**	5.0 ± 0.48**
	Days 22-29	5.7 ± 0.93	5.4 ± 1.13	5.4 ± 0.64	5.2 ± 1.09**	4.7 ± 0.46**
	Days 85-92	5.5 ± 0.87	5.2 ± 0.65	5.4 ± 0.53	5.2 ± 0.54	5.0 ± 1.03**
	Days 169-177	5.2 ± 0.52	5.2 ± 0.63	4.9 ± 0.43	5.0 ± 0.99	4.9 ± 0.87
	Days 367-371	5.5 ± 0.65	5.2 ± 0.81	5.1 ± 0.63*	4.9 ± 0.78**	4.9 ± 0.65**
	Days 535-541	4.5 ± 0.66	4.5 ± 0.60	4.5 ± 0.58	4.1 ± 0.65**	4.1 ± 0.58**
Male body weight (g)	Day 0	26.9 ± 1.48	26.9 ± 1.48	26.9 ± 1.47	26.9 ± 1.49	26.9 ± 1.48
	Day 29	31.1 ± 1.70	30.8 ± 1.86	31.0 ± 1.59	30.7 ± 1.89	30.8 ± 1.91
	Day 92	34.7 ± 2.31	34.7 ± 2.52	34.4 ± 1.93	34.0 ± 1.92	32.8 ± 2.11**
	Day 176	37.8 ± 3.29	37.3 ± 3.57	36.7 ± 2.38	35.7 ± 2.26**	34.2 ± 2.08**
	Day 371	38.6 ± 3.85	39.4 ± 4.05	37.6 ± 3.50	37.1 ± 2.66	35.4 ± 2.12**
	Day 541	39.6 ± 4.03	40.9 ± 4.58	38.9 ± 4.92	38.3 ± 3.60	35.9 ± 2.59**
Male liver weight (12 month sacrifice)	Absolute (g)	1.54 ± 0.175	1.57 ± 0.173	1.84 ± 0.173**	1.95 ± 0.158**	2.25 ± 0.278**
	Relative (% of bw)	4.69 ± 0.540	4.77 ± 0.346	5.58 ± 0.372**	6.11 ± 0.554**	7.49 ± 0.457**
Male liver weight (18 month sacrifice)	Absolute (g)	1.61 ± 0.212	1.72 ± 0.203*	1.73 ± 0.197*	1.85 ± 0.227**	3.06 ± 1.09**
	Relative (% of bw)	4.64 ± 0.589	4.80 ± 0.742	5.15 ± 0.664**	5.50 ± 0.570**	9.90 ± 3.500**

(1) Data are numbers or averages ± SD.
* $P < 0.05$ statistically significant difference from controls, Dunnett's or Mann-Whitney.
** $P < 0.01$ statistically significant difference from controls, Dunnett's or Mann-Whitney.

Table 37. Selected data from mouse chronic study (Naylor and Ruecker 1996). [1]

Group (ppm)		0	100	500	1,500	6,000
Testes weight (12 month sacrifice)	Absolute (g)	0.250 ± 0.0314	0.247 ± 0.0443	0.238 ± 0.0338	0.233 ± 0.0313	0.270 ± 0.0310
	Relative (% of bw)	0.764 ± 0.1062%	0.752 ± 0.1306%	0.725 ± 0.1345%	0.729 ± 0.0782%	0.794 ± 0.0998%
	N	10	9	10	10	10
Testes weight (18 month sacrifice)	Absolute (g)	0.234 ± 0.0408	0.224 ± 0.0353	0.230 ± 0.0312	0.233 ± 0.436	0.233 ± 0.0353
	Relative (% of bw)	0.675 ± 0.1175%	0.628 ± 0.1166%	0.681 ± 0.1258%	0.691 ± 0.1276%	0.754 ± 0.1095%*
	N	45	47	38	43	40

(1) Data are numbers or averages ± SD.
* $P < 0.05$ statistically significant difference from controls, Dunnett's test.

Reyna 1984a

Male and female CD-1 mice were treated with propachlor (purity 96.1%) in feed for up to 90 days. Concentrations were 0, 500, 1,500, and 5,000 ppm. In males, these concentrations corresponded to doses of 0, 87, 260, or 830 mg/kg/d, respectively (calculated by OEHHA staff from data in the report). There were initially 30 animals/sex/group. There was an interim sacrifice of 10 animals/sex/group for hematologic examination around week 7. The remaining animals were sacrificed around week 14. Food consumption, body weight, selected organ weight, and gross and microscopic pathology were reported.

All animals survived until planned sacrifice. Male food consumption was reduced at 5,000 ppm compared to controls for the first three weeks of the study (statistically significant). Male food consumption was lower at 1,500 ppm than controls for the first three weeks of the study (statistically significant only for the third week). Male body weights were reduced in a concentration-related manner across all concentrations from about day 15 onwards (statistically significant at 5,000 ppm, usually statistically significant at 1,500 ppm). Liver weights were increased in a concentration-related manner across all concentrations (statistically significant pairwise for absolute weight at 1,500 and 5,000 ppm and relative weight at all concentrations). See Table 38. The incidence of centrilobular hepatocyte hypertrophy was increased in the 1,500 and 5,000 ppm groups (statistically significant).

Absolute testes weights were lower at 5,000 ppm compared to controls (statistically significant only for right testis). Relative testes weights were similar among groups. See Table 38. Gross and microscopic examination of testes found no propachlor treatment related lesions.

Table 38. Selected male data from mouse subchronic study (Reyna 1984a).

Group (ppm)		0	500	1,500	5,000
Initial number of males		30	30	30	30
Male food consumption (g/kg/d) [1]	Days 1-8	191.5 ± 21.74	189.1 ± 20.51	181.1 ± 22.28	138.2 ± 16.81**
	Days 22-29	183.6 ± 31.60	198.1 ± 39.56	183.1 ± 31.71	185.6 ± 39.25
	Days 50-58	170.1 ± 32.94	159.2 ± 24.96	157.3 ± 27.93	157.0 ± 39.13
	Days 85-92	156.4 ± 38.67	149.8 ± 27.87	152.8 ± 31.27	160.7 ± 41.51
Male body weight (g) [1]	Day 0	28.4 ± 2.00	28.4 ± 2.11	28.4 ± 1.97	28.4 ± 2.04
	Day 29	34.3 ± 2.38	34.0 ± 2.91	33.3 ± 2.23	30.9 ± 2.20**
	Day 58	37.9 ± 2.98	36.6 ± 3.40	35.6 ± 2.64*	33.2 ± 2.80**
	Day 92	38.3 ± 4.16	37.7 ± 3.51	36.6 ± 2.44	34.7 ± 3.06**
Male liver weight [2]	Absolute (g)	2.32 ± 0.054	2.51 ± 0.077	2.89 ± 0.120**	3.43 ± 0.103**
	Relative (% of bw)	5.87 ± 0.109	6.64 ± 0.202#	7.99 ± 0.298#	9.98 ± 0.211#
Right testis weight [2]	Absolute (g)	0.143 ± 0.005	0.132 ± 0.004	0.134 ± 0.003	0.126 ± 0.004**
	Relative (% of bw)	0.363 ± 0.012	0.350 ± 0.012	0.372 ± 0.008	0.366 ± 0.010
Left testis weight [2]	Absolute (g)	0.139 ± 0.004	0.135 ± 0.003	0.132 ± 0.003	0.127 ± 0.004
	Relative (% of bw)	0.351 ± 0.011	0.357 ± 0.009	0.367 ± 0.008	0.369 ± 0.007

(1) Data are averages ± SD. N = 30 up to day 44, n = 20 after day 44.
(2) Data are averages ± SE. N = 20.
* $P < 0.05$ statistically significant difference from controls, ANOVA and Dunnett's test.
** $P < 0.01$ statistically significant difference from controls, ANOVA and Dunnett's test.
# $P < 0.05$ statistically significant difference from controls, Mann-Whitney and Bonferroni.

E.2.2. Studies in rats

Hamada 1987c

Male and female Sprague-Dawley rats were treated with propachlor (96.1% purity) in feed at 0, 10, 50, or 500 ppm for up to two years. In males, this corresponded to doses of 0, 0.48, 2.39, or 23.88 mg/kg/d. There were initially 60 animals/sex/group. After 12 months, 10 animals/sex/group were sacrificed. Surviving animals were sacrificed after 24 months. Survival, body weight and weight gain, food consumption, selected organ weight, and gross and histopathology were reported.

Survival of males was comparable among groups. Total male food consumption for weeks 1-50 was increased in the 50 ppm group compared to controls (statistically significant), but the 10 and 500 ppm groups were similar to controls. Total food consumption for weeks 1-104 was similar among groups. Male body weights were similar among groups. Male liver weights were similar among groups. See Table 39. An increase in the incidence of hepatocyte centrilobular hypertrophy at terminal sacrifice was observed in the high concentration group compared to controls (statistically significant).

Absolute and relative testes with epididymis weights at interim and terminal sacrifice were similar among groups. See Table 40. Gross and microscopic examination of testes and other male reproductive organs found no propachlor treatment related effects.

Table 39. Selected male data from rat chronic study (Hamada 1987c). [1]

Group (ppm)		0	10	50	500
Male survival (adjusted)	Week 14	60/60	60/60	60/60	60/60
	Week 26	60/60	60/60	60/60	60/60
	Week 54	50/50	49/50	49/50	49/50
	Week 78	43/50	46/50	46/50	44/50
	Week 104	29/50	35/50	31/50	31/50
Total male food consumption (g)	Weeks 1-50	4151.5 ± 219.96	4170.7 ± 255.06	4272.5 ± 256.79*	4175.7 ± 249.91
	Weeks 1-104	6545.1 ± 328.95	6531.4 ± 384.00	6588.1 ± 358.14	6581.0 ± 447.33
Male body weight (g)	Week 0	237.0 ± 10.16	234.0 ± 10.37	234.7 ± 11.08	233.3 ± 11.29
	Week 6	443.1 ± 24.41	441.5 ± 25.51	445.6 ± 29.92	438.1 ± 28.49
	Week 14	531.5 ± 32.87	532.0 ± 37.60	538.1 ± 36.48	534.4 ± 40.88
	Week 26	586.1 ± 41.64	590.2 ± 43.56	598.6 ± 41.66	590.0 ± 46.06
	Week 54	649.1 ± 42.58	648.1 ± 57.34	656.6 ± 50.34	650.5 ± 71.50
	Week 78	662.4 ± 88.07	669.6 ± 75.31	676.6 ± 52.49	686.3 ± 81.19
	Week 104	611.3 ± 93.91	597.6 ± 78.36	609.0 ± 81.26	606.6 ± 93.74
Male liver weights (12 month sacrifice)	Absolute (g)	15.21 ± 2.24	15.30 ± 2.72	15.64 ± 1.92	16.23 ± 2.50
	Relative (g/100g bw)	2.51 ± 0.223	2.50 ± 0.403	2.45 ± 0.219	2.67 ± 0.346
	N	10	10	10	10
Male liver weights (24 month sacrifice)	Absolute (g)	14.35 ± 2.33	14.99 ± 3.98	14.36 ± 2.22	14.88 ± 2.76
	Relative (g/100g bw)	2.51 ± 0.473	2.64 ± 0.914	2.47 ± 0.292	2.67 ± 0.851
	N	28	33	30	30

(1) Data are numbers or averages ± SD.
* $P < 0.05$ statistically significant difference compared to controls, ANOVA and Dunnett's or Tukey-Kramer.

Table 40. Selected male data from rat chronic study (Hamada 1987c). [1]

Group (ppm)		0	10	50	500
Testes with epididymides weights (12 month sacrifice)	Absolute (g)	5.73 ± 0.69	5.73 ± 0.59	5.99 ± 0.64	5.64 ± 0.73
	Relative (g/100g bw)	0.956 ± 0.154	0.936 ± 0.120	0.951 ± 0.073	0.937 ± 0.162
	N	10	10	10	10
Testes with epididymides weights (24 month sacrifice)	Absolute (g)	5.29 ± 1.31	5.02 ± 0.86	5.35 ± 1.31	5.17 ± 1.15
	Relative (g/100g bw)	0.916 ± 0.224	0.875 ± 0.149	0.928 ± 0.245	0.910 ± 0.189
	N	28	33	30	30

(1) Data are numbers or averages ± SD.
No statistically significant differences were observed.

Naylor and Thake 1996

Male and female Fischer 344 rats were treated with propachlor (purity 97.83%) in feed at 0, 100, 300, 1,000 or 2,500 (male) or 5,000 (female) ppm for up to two years. Animals in the high concentration group began the study at 1,000 ppm. The concentration was ramped up by 500 ppm per week until the desired final concentration was achieved. In males, these concentrations corresponded to average doses of 0, 5.4, 16.1, 53.6 or 125.3 mg/kg/d. There were initially 60 animals/sex/group. After 12 months, 10 animals/sex/group were sacrificed. Surviving animals were sacrificed after 24 months. Survival, food consumption, body weight and weight gain, selected organ weight, and gross and microscopic pathology results were reported.

Survival of males was similar among groups. Male food consumption in the 1,000 and 2,500 ppm groups was reduced compared to controls at most time periods (usually statistically significant). Male body weights in the 1,000 and 2,500 ppm groups were reduced compared to controls at most time periods after one month of treatment (usually statistically significant). The final body weight for males at 2,500 ppm was about 94% of the control body weight. At the interim (12 month) sacrifice, absolute and relative liver weights were increased at 1,000 and 2,500 ppm compared to controls (statistically significant). At the final (24 month) sacrifice, absolute liver weights were similar between groups, but relative liver weights were higher in the 1,000 and 2,500 ppm groups compared to controls (statistically significant at 2,500 ppm). See Table 41. At the final sacrifice, the incidence of centrilobular/midzonal hepatocellular hypertrophy was increased at 300, 1,000, and 2,500 ppm compared to controls (statistically significant). In the stomach, incidence of erosion/ulceration of the pylorus and herniated mucosal glands was increased at 2,500 ppm compared to controls (statistically significant).

At the interim sacrifice (12 months), absolute and relative testes weights were similar among groups. At the final sacrifice (24 months), absolute and relative testes weights had a concentration-related increase at all concentrations. Absolute testes weights at 2,500 ppm were increased compared to controls (statistically significant). Relative testes weights at 1,000 and 2,500 ppm were increased compared to controls (statistically significant). See Table 42. Gross and microscopic examination of testes and other male reproductive organs found no propachlor treatment related effects at either the 12 or 24 month sacrifices. At the 12 month sacrifice, microscopic examination of the testes found interstitial cell hyperplasia in almost all males in all groups. At the 24 month sacrifice, interstitial cell tumors, aspermia, and bilateral atrophy of the seminiferous tubules were found in almost all males in all groups.

Table 41. Selected male data from rat chronic study (Naylor and Thake 1996). (1)

Group (ppm)		0	100	300	1,000	2,500
Initial number of males		60	60	60	60	60
Males found dead or sacrificed in extremis		13	13	15	12	7
Male food consumption (g/animal/ day)	Days 1-9	15.6 ± 0.92	15.2 ± 0.84*	14.9 ± 0.95**	14.3 ± 0.96**	14.1 ± 0.88**
	Days 23-30	17.1 ± 1.09	16.7 ± 1.49	17.0 ± 0.87	16.5 ± 0.87*	15.2 ± 0.85**
	Days 87-93	15.3 ± 0.94	15.1 ± 0.96	15.0 ± 0.76	14.9 ± 0.92*	14.0 ± 0.96**
	Days 171-178	17.1 ± 1.08	16.7 ± 0.84	16.9 ± 0.76	16.9 ± 0.98	15.8 ± 0.79**
	Days 367-374	18.4 ± 1.58	19.0 ± 1.51	18.3 ± 1.46	18.0 ± 1.44	16.9 ± 1.08**
	Days 722-730	17.5 ± 2.18	17.6 ± 3.07	17.6 ± 2.33	17.3 ± 2.12	16.2 ± 1.78*
Male body weight (g)	Day 0	111.6 ± 7.57	111.6 ± 7.61	111.6 ± 7.60	111.7 ± 7.63	111.7 ± 7.64
	Day 30	232.4 ± 11.28	233.6 ± 12.54	234.3 ± 13.17	224.6 ± 11.87**	213.1 ± 10.08**
	Day 93	317.7 ± 15.52	315.8 ± 17.61	313.6 ± 17.05	304.2 ± 17.28**	281.5 ± 15.67**
	Day 178	365.4 ± 17.60	366.8 ± 19.83	364.3 ± 17.46	354.3 ± 18.99**	328.0 ± 17.48**
	Day 374	403.1 ± 21.67	414.4 ± 21.68*	408.3 ± 19.17	396.2 ± 25.26	365.6 ± 21.09**
	Day 730	372.5 ± 35.16	373.9 ± 42.92	370.6 ± 40.86	361.9 ± 32.41	348.2 ± 22.80**
Male liver weight (12 month sacrifice)	Absolute (g)	10.49 ± 1.062	11.08 ± 1.249	10.80 ± 0.942	12.02 ± 1.061**	11.92 ± 0.968*
	Relative (% of bw)	2.74 ± 0.230	2.83 ± 0.130	2.76 ± 0.201	3.08 ± 0.242*	3.47 ± 0.129**
Male liver weight (24 month sacrifice)	Absolute (g)	12.34 ± 2.424	12.90 ± 2.769	12.04 ± 2.198	12.45 ± 2.098	12.28 ± 1.358
	Relative (% of bw)	3.58 ± 0.785	3.69 ± 0.699	3.49 ± 0.508	3.72 ± 0.720	3.75 ± 0.310**

(1) Data are numbers or averages ± SD.
* $P < 0.05$ statistically significant difference from controls, Dunnett's test.
** $P < 0.01$ statistically significant difference from controls, Dunnett's test.

Table 42. Selected male data from rat chronic study (Naylor and Thake 1996). (1)

Group (ppm)		0	100	300	1,000	2,500
Testes weight (12 month sacrifice)	Absolute (g)	3.22 ± 0.157	3.23 ± 0.293	3.17 ± 0.325	3.28 ± 0.157	3.13 ± 0.445
	Relative (% of bw)	0.845 ± 0.0520	0.827 ± 0.0678	0.813 ± 0.1024	0.841 ± 0.0348	0.913 ± 0.1141
	N	10	10	10	10	10
Testes weight (24 month sacrifice)	Absolute (g)	4.41 ± 1.969	4.62 ± 2.134	5.06 ± 1.964	5.48 ± 2.160	5.87 ± 1.915**
	Relative (% of bw)	1.257 ± 0.5369	1.311 ± 0.5726	1.451 ± 0.5241	1.615 ± 0.5969*	1.767 ± 0.5634**
	N	37	37	35	38	41

(1) Data are numbers or averages ± SD.
* $P < 0.05$ statistically significant difference from controls, Dunnett's test.
** $P < 0.01$ statistically significant difference from controls, Dunnett's test.

Reyna 1984b

Male and female Sprague-Dawley rats were treated with propachlor (96.1% purity) in the diet for up to 3 months. The target concentrations were 0, 300, 1,500, and 7,500 ppm. In males, these concentrations corresponded to doses of 0, 21, 100, or 490 mg/kg/d, respectively (calculated by OEHHA staff from data in the report). There were initially 30 animals/sex/group. An interim sacrifice of 10 animals/sex/group was performed after 6 weeks of treatment. Survival, food consumption, body weight, selected organ weights, and gross and microscopic pathology results were reported.

All animals survived to scheduled sacrifices. Male food consumption on a g food/kg body weight basis was reduced at 7,500 ppm compared to controls up to about week 4 of treatment (statistically significant) and increased compared to controls after about week 7 of treatment (statistically significant). Male body weight was reduced at 1,500 and 7,500 ppm compared to controls (92% and 41% of controls at end of treatment, respectively, statistically significant). Several male absolute organ weights were reduced, but relative organ weights were increased at 7,500 ppm compared to controls (some statistically significant). Relative liver weights were increased at 1,500 ppm compared to controls (statistically significant). See Table 43. Gross and microscopic examinations of non-reproductive organs found no propachlor treatment related effects, with the exception of very small spleens at 7,500 ppm.

Absolute testes weight was reduced and relative testes weight was increased at 7,500 ppm (both statistically significant). See Table 43. Gross and microscopic examinations of testes and epidiymides found no propachlor treatment related effects.

Table 43. Selected male data from rat subchronic study (Reyna 1984b).

Group (ppm)		0	300	1,500	7,500
Initial number of males		30	30	30	30
Male food consumption (g/kg/d) [1]	Days 1-7	107.4 ± 6.24	107.5 ± 8.03	101.1 ± 22.37	42.7 ± 12.00**
	Days 21-28	76.5 ± 4.41	75.7 ± 3.91	75.2 ± 4.31	70.2 ± 14.83*
	Days 49-56	62.5 ± 4.09	61.5 ± 2.73	60.1 ± 2.08	69.9 ± 16.26*
	Days 84-91	51.9 ± 2.73	53.0 ± 4.08	54.4 ± 6.97	65.3 ± 21.67**
Male body weight (g) [1]	Day 0	157.3 ± 9.73	157.1 ± 9.82	157.3 ± 10.05	157.1 ± 10.38
	Day 28	342.1 ± 20.77	340.4 ± 25.90	323.0 ± 24.90**	144.5 ± 12.77**
	Day 56	435.1 ± 29.54	434.5 ± 37.22	401.4 ± 30.16**	178.3 ± 17.64**
	Day 91	496.4 ± 35.94	502.8 ± 47.55	456.2 ± 38.06**	202.2 ± 21.42**
Male liver weight [2]	Absolute (g)	14.36 ± 0.405	15.35 ± 0.464	14.67 ± 0.582	9.30 ± 0.303**
	Relative (% of bw)	3.02 ± 0.065	3.23 ± 0.075	3.43 ± 0.114#	5.02 ± 0.134#
Testes weight [2]	Absolute (g)	5.26 ± 0.123	5.42 ± 0.097	4.97 ± 0.132	3.99 ± 0.077**
	Relative (% of bw)	1.11 ± 0.025	1.15 ± 0.028	1.17 ± 0.037	2.17 ± 0.060#

(1) Data are averages ± SD. N = 30/group up to day 35, n = 20/group after day 35.
(2) Data are averages ± SE. N = 20/group.
* $P < 0.05$ statistically significant difference from controls, ANOVA and Dunnett's test.
** $P < 0.01$ statistically significant difference from controls, ANOVA and Dunnett's test.
# $P < 0.05$ statistically significant difference from controls, Mann-Whitney and Bonferroni.

Rush 1998

Male and female Sprague-Dawley rats were treated dermally with propachlor (98.25% purity) for 5 days per week for 3 weeks. Doses were 0, 40, 150, or 500 mg/kg/d. Propachlor was dissolved in acetone and applied to the shaved dorsal surface of the rats in a volume of 5 ml/kg body weight. The application site was covered with gauze and elastic wrap. The propachlor solution was applied for 6 hours and then removed and the application site wiped with gauze soaked in water. There were 10 rats/sex/group. Rats were sacrificed on day 22 or 23. Survival, clinical signs, body weight and weight gain, food consumption, selected organ weights, and selected gross and microscopic pathology were reported.

All animals survived to scheduled sacrifice. Dermal reactions were characterized by the author as minimal to mild, and occurred mainly in the 150 and 500 mg/kg/d groups, although some also occurred in the control group. These reactions included erythema, edema, eschar (sloughing of necrotic tissue), and desquamation. Male food consumption was slightly lower in the 500 mg/kg/d group compared to controls for weeks two and three (not statistically significant). Male body weight was slightly lower in the 500 mg/kg/d group compared to controls by the end of the study (not statistically significant). Male body weight gain was reduced at 500 mg/kg/d compared to controls for week three (statistically significant). Male liver weights were similar among groups. See Table 44. Microscopic examination of the livers of 500 mg/kg/d and control groups found no propachlor treatment related effects.

Testes weights were similar among groups. See Table 44. No gross lesions of the testes were observed. Microscopic examination of the testes was not performed.

Table 44. Selected male data from rat dermal study (Rush 1998). [1]

Group (mg/kg/d)		0	40	150	500
Number of females		10	10	10	10
Male food consumption (g/animal/d)	Days 1-8	28 ± 2.0	30 ± 2.4	29 ± 1.1	27 ± 1.6
	Days 8-15	32 ± 2.2	33 ± 2.7	32 ± 1.5	30 ± 2.4
	Days 15-21	33 ± 2.4	32 ± 2.3	32 ± 1.8	31 ± 2.9
Male body weight (g)	Day –1	200 ± 12.7	202 ± 12.3	202 ± 10.3	200 ± 10.5
	Day 8	265 ± 15.6	265 ± 22.2	265 ± 12.4	263 ± 14.2
	Day 15	311 ± 17.9	314 ± 28.8	313 ± 15.1	309 ± 18.3
	Day 21	341 ± 21.7	341 ± 30.2	337 ± 18.4	329 ± 18.9
Male body weight gain (g)	Days –1-8	66 ± 5.1	63 ± 10.8	62 ± 7.2	62 ± 5.6
	Days 8-15	46 ± 6.5	49 ± 7.7	48 ± 6.6	46 ± 5.9
	Days 15-21	30 ± 6.4	27 ± 5.6	24 ± 4.9	21 ± 5.8**
Male liver weight	Absolute (g)	11.75 ± 0.968	11.59 ± 1.001	11.08 ± 0.807	11.35 ± 1.196
	Relative (% of bw)	3.91 ± 0.211	3.82 ± 0.193	3.68 ± 0.182	3.86 ± 0.283
Testes weight	Absolute (g)	3.20 ± 0.236	3.16 ± 0.173	3.38 ± 0.252	3.30 ± 0.285
	Relative (% of bw)	1.07 ± 0.089	1.05 ± 0.083	1.13 ± 0.091	1.12 ± 0.092

(1) Data are numbers or averages ± SD.
** $P < 0.01$ statistically significant difference from controls, ANOVA and Tukey-Kramer.

Zlateva and Maleva (1979)

This study was published in Bulgarian, with an English summary. Partial translation of the text was performed by OEHHA staff.

Male Wistar rats were treated by gavage with a water suspension of Ramrod (a commercial preparation of propachlor, purity not stated in this paper) for 4 or 6 months. The doses were stated to be 0 (control), $1/200^{th}$, $1/100^{th}$, or $1/20^{th}$ of the LD_{50}. The LD_{50} was assumed by the authors to be 1,200 mg/kg, based upon information supplied by the manufacturer. Corresponding doses would be 0, 6, 12, or 60 mg/kg/d. There were 10 males/group. Males were sacrificed and the testes were fixed, stained, and examined microscopically. Results presented in this paper included two micrographs, but no numerical data.

No data on systemic toxicity were reported. The authors reported that, in males treated for 4 months, disruption of spermatogenesis was observed under the capsule (i.e. near the periphery) of the testicles. In particular, spermatogenesis was normal in the early stages, but subsequent maturation was not. In some areas, tubules were clogged with degenerating cells, and in some areas the epithelium was separated from the basal membrane. Sertoli cells were less impacted than spermatogenic cells. Blood vessels were thickened throughout the testicles. The dose(s) at which these observations were made were not clear.

In males treated for 6 months, disruption of spermatogenesis was more pronounced. Spermatogenesis ceased at the spermatid stage. Disturbances of meiotic and mitotic division were observed. The basal membrane was thin, and spermatogenic cells were separated from the membrane and free in the lumen. Numbers of spermatogonia were reduced, and giant multinucleated cells were common. Sertoli cells were also affected. Blood vessels had thickened walls and disturbed structure. The most pronounced effects were observed at the high dose.

E.2.3. Studies in dogs

Naylor and Ruecker 1985

Male and female beagle dogs were treated with propachlor (96.1% purity) in feed at 0, 100, 500, or 1,500 ppm for 90 days. In females, this corresponded to 0, 4, 20,or 42 mg/kg/d, respectively. Dogs in the high concentration group were fed 750 ppm for the first week, then 1,500 ppm thereafter. There were 6 animals/sex/group. Body weight and weight gain, organ weights, and gross and microscopic pathology were reported.

In males, reduced food consumption and body weight gain in all propachlor treated groups compared to controls were observed. See Table 45.

Testes weights were similar among groups. See Table 45. Testes with epididymides were examined for gross and microscopic pathology. No propachlor treatment related effects were observed.

Table 45. Selected male data from dog subchronic study (Naylor and Ruecker 1985). [1]

Group (ppm)		0	100	500	1,500
Number of males		6	6	6	6
Male food consumption (g/animal/d) [1]	Study days 1-7	363.3	343.6	337.1	297.1
	Study days 14-21	388.0	368.9	357.3	250.8
	Study days 49-56	396.6	372.0	355.9	324.7
	Study days 84-90	400.0	374.4	378.3	327.1
	Average: study days 1-90	394.4	364.5	361.6	298.2
Male body weight (kg) [2]	Study day 0	8.6 ± 1.41	8.5 ± 1.04	8.6 ± 1.09	8.5 ± 1.21
	Study day 21	9.2 ± 1.54	8.9 ± 1.35	8.6 ± 1.44	8.4 ± 0.88
	Study day 56	9.8 ± 1.53	9.3 ± 1.94	8.8 ± 2.24	8.9 ± 1.01
	Study day 90	10.1 ± 1.46	9.2 ± 2.16	8.6 ± 1.43	9.1 ± 1.20
Male body weight gain (%)		16.1%	8.2%	1.2%	7.1%
Testes weight [3]	Absolute (g)	16.521 ± 0.777	15.578 ± 2.343	16.426 ± 2.591	17.981 ± 0.541
	Relative (g/100 g bw)	0.170 ± 0.010	0.166 ± 0.021	0.186 ± 0.026	0.202 ± 0.014

(1) Averages (indices of variation, e.g. SD, were not reported).
(2) Average ± SD.
(3) Average ± SE.
No statistically significant differences were observed.

Naylor and Ruecker 1986

Male and female beagle dogs were treated with propachlor (97.1% purity) in feed for one year. Nominal concentrations were 0, 25, 250, or 1,000 ppm. Analytical concentrations were 0, 24, 240, or 970 ppm, respectively. In males, this corresponded to doses of 0, 0.9, 10.1, and 33.2 mg/kg/d, respectively. Animals in the two highest concentration groups were ramped up to the final concentration over a three week period. There were 6 animals/sex/group. Survival, food consumption, body weight and weight gain, organ weights, and gross and microscopic pathology results were reported.

All animals survived to terminal sacrifice. In males, food intake was lower in the high concentration group than in controls (not generally statistically significant). The authors attributed this to poor feed palatability at the high propachlor concentration. In the high concentration group, males gained less weight initially, and remained at lower weights throughout the study compared to controls (final weight 87% of controls) (not statistically significant). See Table 46.

Testes weights were similar among groups. See Table 46. Gross and microscopic examination of testes found no lesions attributable to propachlor treatment.

Table 46. Selected male data from dog chronic study (Naylor and Ruecker 1986). (1)

Group (ppm)		0	25	250	1,000
Number of males		6	6	6	6
Male food consumption (g/animal/ day) (1)	Study days 1-8	292.9	267.7	296.2	287.4
	Study days 22-29	299.9	333.0	336.8	256.4
	Study days 78-86	330.6	369.6	376.7	286.5
	Study days 162-170	314.6	373.1	385.0	295.4
	Study days 379-386	308.6	336.3	363.6	294.9
Male body weight (kg) (2)	Study day 0	7.6 ± 0.80	7.6 ± 0.80	7.6 ± 0.89	7.6 ± 0.72
	Study day 29	8.2 ± 0.91	8.3 ± 0.93	8.1 ± 1.18	7.8 ± 0.68
	Study day 86	9.5 ± 1.22	9.4 ± 1.07	9.1 ± 1.41	8.4 ± 0.92
	Study day 170	10.1 ± 1.71	9.7 ± 2.44	9.9 ± 1.64	8.9 ± 1.00
	Study day 386	11.0 ± 1.52	11.6 ± 2.27	10.6 ± 2.02	9.6 ± 0.92
Testes weight at sacrifice (3)	Absolute (g)	19.817 ± 0.814	21.933 ± 1.033	20.117 ± 1.596	18.550 ± 1.466
	Relative (g/100 g bw)	0.177 ± 0.008	0.196 ± 0.016	0.197 ± 0.011	0.197 ± 0.008

(1) Average (indices variation, e.g. SD, not reported)
(2) Average ± SD.
(3) Average ± SE.
No statistically significant differences were found.

E.3. Other relevant data

Zlateva et al. 1978

In this study, male Wistar rats were treated with "Ramrod," a commercial preparation containing propachlor. The fraction of the preparation which was propachlor was not stated. Treatment was by gavage of an aqueous suspension of Ramrod at 0, 12, or 60 mg/kg/d for 4 or 6 months. There were initially 20 males/group. Half of each group were sacrificed at the end of the treatment period, and half were sacrificed after a one month recovery period. The study also examined the effects of vibration, but those results are not summarized herein. The results of assays for ATPase activity in the testes of 6 rats per group were reported. No data on other effects were reported.

In male rats treated with Ramrod for 4 months, reduced testicular ATPase activity compared to controls was observed (about 50% of controls, statistically significant). ATPase activity for both doses of Ramrod were similar: no dose response was apparent. After a one month recovery period, the ATPase activities were close to controls, but still slightly lower (statistically significant). In rats treated with Ramrod for 6 months, increased testicular ATPase activity compared to controls was observed (about 2 to 3 times the control value, statistically significant). After a one month recovery period, the ATPase activities were close to controls, but still slightly higher (statistically significant). See Table 47.

Table 47. Results from male rat study (Zlateyev et al. 1978). (1)

Treatment group (dose Ramrod, duration)	0 mg/kg/d 4 or 6 months?	12 mg/kg/d 4 months	60 mg/kg/d 4 months	12 mg/kg/d 6 months	60 mg/kg/d 6 months
Results after treatment period					
ATPase activity (2)	0.0060 ± 0.0009	0.0030 ± 0.0016**	0.0028 ± 0.0003***	0.0137 ± 0.0013***	0.0185 ± 0.0027***
Results after one month recovery period					
ATPase activity (2)	0.0060 ± 0.0005	0.0058 ± 0.0018**	0.0056 ± 0.0008**	0.0061 ± 0.0007*	0.0064 ± 0.0013*

(1) Data are numbers or averages (± SD or SE not reported).
(2) mg P/100 g protein.
* $P < 0.05$ statistically significant difference compared to controls, Student-Fisher.
** $P < 0.01$ statistically significant difference compared to controls, Student-Fisher.
*** $P < 0.001$ statistically significant difference compared to controls, Student-Fisher.

E.4. Male reproductive toxicity: integrative evaluation

Data relevant to the potential male reproductive toxicity of propachlor are available from two rat reproductive toxicity studies and a rat male dominant lethal study. Additionally, there are several subchronic or chronic studies in mice, rats, and dogs which have some relevant data.

In a rat reproductive toxicity study (Groya 1986), male and female Fisher 344 rats were treated with propachlor in food at concentrations adjusted to give doses of 0, 0.3, 3.0, or 30 mg/kg/d for two generations. Male systemic toxicity was observed in the F1 generation in the forms of reduced food consumption and body weight in the 30 mg/kg/d group compared to controls (statistically significant). In the F0/F1 litter, fertility (fraction of females pregnant) was reduced in the 3.0 mg/kg/d group compared to controls (statistically significant), but fertility in the 30 mg/kg/d group was similar to the controls. In the F1/F2a litter, fertility was lower in the 3.0 and 30 mg/kg/dgroups than in controls (statistically significant for the 3.0 mg/kg/d group only). In the F1/F2b litter, fertility was similar among groups. For all litters, litter sizes were similar among groups.

In a later rat reproductive toxicity study (Lemen and Thake 1995), male and female Sprague-Dawley rats were treated with propachlor in food at concentrations of 0, 100, 1,000, or 2,500 (male) or 5,000 (female) ppm for two generations. For males, these concentrations corresponded to average doses of about 0, 7, 70, and 166 mg/kg/d. Male systemic toxicity was observed in the F0 generation in the forms of reduced food consumption and body weight in the 1,000 and 2,500 ppm groups compared to controls (often statistically significant). Similar effects were observed in the F1 generation in the 1,000 ppm group. The 2,500 ppm group was discontinued after the first generation due to severe adverse effects on pups during lactation. No adverse effects were observed on precoital length, percentage of males copulating, percentage of males impregnating females, or fertility (percentage of females pregnant). In the F0/F1 litter, live litter size at birth was reduced in the 2,500 ppm group compared to controls (statistically significant). These pups also had reduced survival during lactation compared to controls.

In the male dominant lethal study (Naylor 1994), male Sprague-Dawley rats were treated with propachlor in food at concentrations of 0, 300, 1,000, or 2,500 ppm for approximately 10 weeks before mating and for two rounds of mating with untreated females. These concentrations corresponded to doses of 0, 13.6, 43.9 or 111.8 mg/kg/d, respectively. Male systemic toxicity was observed in the forms of reduced food consumption, body weight, and body weight gain in the 1,000 and 2,500 ppm groups (statistically significant). No propachlor treatment related effects were observed on male fertility, percentage of females pregnant, total implantations, viable implantations, or resorptions (i.e. no dominant lethal effects were observed).

Several studies have examined the effects of propachlor treatment on testes weight. These include studies in mice, rats, and dogs. Absolute testes weight was increased in some studies, decreased in some studies, and similar among groups in other studies. In a few studies the increases or decreases were statistically significant. Relative testes weight was increased in several, but not all, studies. Some of the increases were statistically significant. These increases were in part due to decreased body weight.

Two studies found statistically significant decreases in absolute testes weights. These were subchronic studies in mice (Reyna 1984a) and rats (Reyna 1984b). Statistically significant reductions in absolute testes weights were observed only at the highest concentrations tested (5,000 and 7,500 ppm, respectively). In both studies, statistically significant reductions in body weights were also found at these concentrations. In the mouse study, relative testes weights were not affected. In the rat study relative testes weights were increased in the highest concentration group (statistically significant). Neither study found propachlor-treatment related gross or microscopic lesions of the testes.

One study found a statistically significant increase in absolute testes weight. This was a chronic study in rats (Naylor and Thake 1996). The highest concentration tested in this study was 2,500 ppm. There was no effect on absolute or relative testes weights at the 12 month sacrifice. Both absolute and relative testes weights were increased at the 24 month sacrifice (statistically significant at 2,500 ppm). Gross and microscopic examination found no propachlor-treatment related lesions of the testes. However, microscopic examination found interstitial cell tumors, aspermia, and bilateral atrophy of the seminiferous tubules in almost all males in all groups.

Several studies have reported the results of gross and/or microscopic examination of testes and sometimes other male reproductive organs. These also include studies in mice, rats, and dogs.

A rat subchronic study published in Bulgarian (Zlateva and Maleva 1979) has been partially translated by OEHHA staff. This study was poorly reported. In this study, male Wistar rats were treated for 4 or 6 months by gavage with a water suspension of Ramrod, a commercial preparation of propcahlor. The percentage of Ramrod which was propachlor was not reported in this paper, although another paper (also in Bulgarian) indicated a purity of 65% (Mirkova 1975). OEHHA staff has no information on the other components of Ramrod. The doses used were not clearly reported; the doses appear to have been 0, 6, 12, or 60 mg/kg/d, although it is not clear if this refers to Ramrod or propachlor. No information on male systemic effects was reported. Based on the partially translated results, treatment at unspecified doses appeared to cause disruption of spermatogenesis, sloughing of seminiferous epithelium, germ cell degeneration, and structural changes in testicular blood vessels. In a related study (published in English), Zlateva et al. (1978) observed reduced testicular ATPase activity after 4 months of treatment with Ramrod at doses similar to those used by Maleva and Zlateva (1979). After 6 months of treatment, increased testicular ATPase activity was observed.

None of the other studies found adverse gross or microscopic effects on testes or other male reproductive organs. The other studies used propachlor with reported purities around 95% to 98%. Most of the other studies used treatment in food, and some used concentrations resulting in higher doses than those used in the study by Zlateva and Maleva (1979). In most of the other studies, mild to severe male systemic toxicity (e.g. reduced food consumption and/or weight gain) was observed.

In summary, in a rat oral reproductive study, sporadic reductions in fertility were observed. However, these were not dose-related, and were not observed in a later rat oral reproductive study which used similar and much higher concentrations of propachlor. In the later rat reproductive study, the F0/F1 high concentration group had reduced live litter size at birth and

reduced pup survival during lactation. The high concentration group was discontinued after the first generation. The reduction of live litter size could be indicative of a dominant lethal type effect. A male dominant lethal study in rats was conducted with males treated at similar concentrations and for similar durations to the males in the later two-generation reproduction study. No effects on male fertility, females becoming pregnant, total implantations, viable implantations, or resorptions were observed. Since both males and females were treated in the two-generation reproduction study, the effects observed in the two-generation study are likely to be due to the treatment of females (i.e. developmental or female reproductive effects).

One poorly reported study (partially translated from Bulgarian) found disruption of spermatogenesis (observed microscopically) in rats treated with Ramrod, a commercial preparation of propachlor. However, numerous other well reported studies, using propachlor of much better purity and sometimes at higher doses, found no adverse gross or microscopic effects on testes.

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