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.

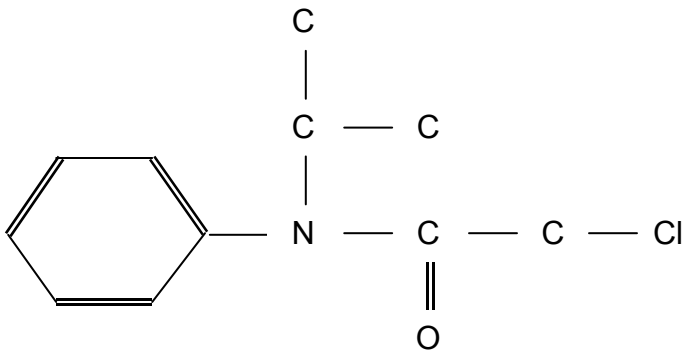
In some studies, increases or decreases in absolute testes weight were observed (a few statistically significant). In several studies, relative testes weights were increased, in part due to reduced body weights (sometimes statistically significant). Reduced absolute testes weights (statistically significant) 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

weight, and stomach lesions. There was a possible indication of neurotoxicity in an acute study, but no indication of neurotoxcity in a subchronic study.

C. Developmental Toxicity

No studies in humans providing data on the potential developmental toxicity of propachlor were located by OEHHA staff. Three rabbit developmental toxicity studies (one range-finding and two main studies) and three rat developmental toxicity studies (one range-finding and two main studies) were located. In addition, two rat reproductive toxicity studies with data relevant to developmental toxicity were located. One of the rat developmental studies was published in the open literature; the remainder of the studies were conducted for pesticide registration purposes and have not been published.

C.1. Developmental toxicity studies

C.1.1 Developmental toxicity studies in rabbits

Schardein 1984, Keller 1987

In this study, artificially inseminated New Zealand White rabbits were treated with propachlor (purity 96.5%) in a corn oil suspension by gavage at 0, 5, 15, or 50 mg/kg/d for gestation days (gd) 7-19. There were 16 inseminated females per group. Surviving females were sacrificed on gd 29. Females that died during the study were given a gross necropsy. Maternal survival, clinical signs, and body weight were reported. Abortions, corpora lutea, implantations, post-implantation losses, fetal body weight, and external, soft tissue, and skeletal fetal anomalies were reported.

A total of 10 females died during the study. Two of these died before administration of propachlor began (one in the low dose group, one in the mid dose group). There was no apparent dose-response relationship with deaths (2 , 3, 3 , and 2 deaths in the control, 5, 15, and 50 mg/kg/d groups, respectively). The cause(s) of deaths were not determined. Congested or "consolidated" lungs were observed in the majority of females that died during the study. Congested lungs were also observed in several females that survived to sacrifice. Female body weights, body weight gains, and adjusted body weights (i.e. minus uterus) were similar among groups. See Table 1.

Abortions occurred late in gestation in two 5 mg/kg/d and one 15 mg/kg/d group females. The numbers of corpora lutea were similar among groups. Pre- and post-implantation losses were elevated in the 15 and 50 mg/kg/d groups compared to controls (not statistically significant). Live litter size was smaller in the 15 and 50 mg/kg/d groups than controls (statistically significant only in the mid dose group). See Table 1. Gross and soft-tissue malformations were similar among groups. Total malformations were increased in the 15 mg/kg/d group compared to controls (statistically significant for litter, not for fetus). This mainly consisted of an increase in skeletal malformations. The specific skeletal malformations observed in the 15 mg/kg/d group were costal cartilage anomaly, sternoschisis, centra anomaly, vertebral anomalies, and bent rib.

Each was observed in one or two fetuses in this group. Centra and vertebra anomalies were also observed in the 50 mg/kg/d group. See Table 2. Fetal variations were similar among groups.

Table 1. Selected data from rabbit developmental study (Schardein 1984, Keller 1987).[1]

Group (mg/kg/d)		0	5	15	50
Inseminated females		16	16	16	16
Female deaths		2	3	3	2
Females aborting		0	2	1	0
Females alive, not aborted by gd 29		14	11	12	14
Body weight (g)	gd 0	3855 ± 262.7	3914 ± 280.6	3816 ± 217.2	3837 ± 204.1
	gd 7	3977 ± 263.5	4051 ± 316.3	3940 ± 251.6	3990 ± 212.2
	gd 19	4111 ± 424.8	4144 ± 391.4	4001 ± 305.3	4128 ± 227.2
	gd 29	4218 ± 373.3	4298 ± 422.2	4113 ± 370.8	4244 ± 243.3
	gd 29 adjusted [2]	3781 ± 343.3	3920 ± 372.3	3821 ± 287.0	3903 ± 254.2
Non-pregnant females at sacrifice		2	3	1	0
Pregnant females at sacrifice		12	8	11	14
Females with total resorptions		0	0	1	1
Corpora lutea/litter		11.4 ± 2.31	13.0 ± 3.63	12.7 ± 3.06	13.0 ± 5.53
Implantations/litter		8.6 ± 1.93	8.3 ± 1.91	6.6 ± 2.62	7.0 ± 1.92
Post-implantation loss/litter [3]		0.6 ± 0.90	0.4 ± 0.74	1.4 ± 1.29	1.1 ± 1.41
Live fetuses/litter [3]		8.0 ± 1.65	7.9 ± 2.59	5.2 ± 2.27*	5.9 ± 2.66
Pre-implantation loss (%) [4]		24.8%	36.5%	42.5%	46.2%
Post-implantation loss (%) [3, 4]		6.8%	4.5%	21.9%	16.3%
Fetal weight [5]		37.9 ± 4.86	34.4 ± 5.09	38.5 ± 4.57	38.6 ± 4.95

(1) Data are numbers, averages ± SD, or percentages.
(2) Body weight minus gravid uterus weight.
(3) Includes females with total resorptions.
(4) Group percentage.
(5) Litter average ± SD.
* $p < 0.05$ statistically significant difference from controls. ANOVA, Dunnett's test.

Table 2. Selected data from rabbit developmental study (Schardein 1984, Keller 1987). (1)

Group (mg/kg/d)		0	5	15	50
Litters examined for malformations		12	8	10	13
Fetuses examined externally		96	63	58	82
Fetuses examined viscerally		96	63	58	82
Fetuses examined skeletally		96	63	57	82
Total malformations [fetuses (litters)]		0	3 (2)	7 (6**)	3 (3)
External malformations [fetuses (litters)]		0	1 (1)	2 (2)	0
Visceral malformations [fetuses (litters)]		0	0	1 (1)	0
Skeletal malformations [fetuses (litters)]		0	2 (2)	5 (5)	3 (3)
Specific skeletal malformations [fetuses (litters)]	Forked scapula	0	1 (1)	0	0
	Costal cartilage anomaly	0	0	1 (1)	0
	Fused sternebrae	0	1 (1)	0	0
	Sternoschisis	0	0	1 (1)	0
	Centra anomaly	0	0	1 (1)	1 (1)
	Vertebral anomaly	0	0	2 (2)	2 (2)
	Bent rib	0	0	1 (1)	0

(1) Data are numbers.
** $p < 0.01$ statistically significant difference from controls. Chi-square or Fisher's Exact test.

Adam 1992, Mercieca 1992 (range-finding study)

There were two studies in this report. The first was a range finding study, and the second a main study. The two studies were performed in different labs, but used the same strain of rabbit, and the same dosing period. The main study was performed soon after the pilot study.

In the range-finding study, inseminated female New Zealand White rabbits were treated by gavage with propachlor (purity 96.8%) suspended in 0.5% methylcellulose in water for gd 7-19. The doses were 0, 25, 75, 125, 175, or 225 mg/kg/d. There were 7 females per group. Animals that did not die, were not sacrificed moribund, and did not abort were sacrificed on gd 29. Results were reported for female survival, clinical signs, body weight, and gross necropsy. Abortions, uterine weight, corpora lutea, implantations, resorptions, fetal death, fetal body weight, and fetal malformations were reported.

At 225 mg/kg/d (the highest dose), all 7 females died or were sacrificed moribund within three days of the beginning of propachlor administration. At 175 mg/kg/d, 5 out of 7 females died or were sacrificed moribund during the dosing period. At 125 mg/kg/d, 3 out of 7 females died during the dosing period. No females in the lower dose groups died. The cause of death was not determined, except for one female in the 125 mg/kg/d group that appeared to die from gavage error. Females that died displayed reduced defecation and soft stools. Due to early deaths or sacrifices, no body weight data were available for the 225 mg/kg/d group during the dosing period. Females in the 125 and 175 mg/kg/d groups lost weight during the dosing period (statistically significant difference from controls). Body weight and weight gain at sacrifice was lower than controls in the 125 mg/kg/d group (not statistically significant). Body weight and weight gain during the dosing period and at sacrifice were similar in the control and the 25 and 75 mg/kg/d groups. There were no statistically significant differences in liver, kidney, or spleen weights at sacrifice between the controls and the 25, 75, and 125 mg/kg/d groups. See Table 3.

One female each in the 25 and 175 mg/kg/d groups aborted. The only female in the 175 mg/kg/d group that did not die, was not sacrificed moribund, or abort, was not pregnant. There were no statistically significant differences between the controls and the 25, 75, and 125 mg/kg/d groups for corpora lutea, implantation sites, pre-implantation loss, early or late resorptions, dead fetuses, post-implantation losses, viable fetuses, or fetal weights. No gross external abnormalities were observed. See Table 4.

Table 3. Selected data, rabbit range-finding developmental study (Adam 1992, Mercieca 1992). [1]

Group (mg/kg/d)		0	25	75	125	175	225
Inseminated females		7	7	7	7	7	7
Females that died or were sacrificed moribund		0	0	0	3	5	7
Female body weights (g)	gd 0	3384 ± 168	3252 ± 138	3279 ± 248	3276 ± 159	3435 ± 342	3452 ± 217
	gd 7	3730 ± 178	3675 ± 185	3665 ± 174	3651 ± 161	3785 ± 316	3788 ± 236
	gd 10	3794 ± 141	3733 ± 198	3665 ± 194	3514 ± 129	3425 ± 291*	ND
	gd 19	4017 ± 110	3981 ± 207	3940 ± 236	3573 ± 120*	2484 ± 0	ND
	gd 29	4040 ± 222	4017 ± 314	3865 ± 201	3639 ± 133	ND	ND
	gd 29 net [2]	3693 ± 275	3646 ± 250	3635 ± 252	3323 ± 168	ND	ND
Female body weight change (g)	gd 0-7	345 ± 95	423 ± 53	386 ± 133	374 ± 48	350 ± 74	336 ± 92
	gd 7-10	64 ± 46	58 ± 31	-1 ± 41	-136 ± 86**	-360 ± 101**	ND
	gd 7-19	287 ± 112	307 ± 32	275 ± 96	-88 ± 202**	-1045 ± 0	ND
	gd 19-29	24 ± 175	48 ± 118	-76 ± 157	65 ± 76	ND	ND
	gd 0-29	656 ± 214	775 ± 173	585 ± 256	370 ± 259	ND	ND
	gd 0-29 net [2]	308 ± 255	404 ± 111	356 ± 377	55 ± 84	ND	ND

(1) Data are numbers or averages ± SD.
(2) Body weight minus uterus weight.
ND: No Data (all animals died, were sacrificed moribund, were not pregnant, or aborted).
* $P < 0.05$ statistically significant difference from controls, Dunnett's test.
** $P < 0.01$ statistically significant difference from controls, Dunnett's test.

Table 4. Selected data, rabbit range-finding developmental study (Adam 1992, Mercieca 1992). [1]

Group (mg/kg/d)	0	25	75	125	175	225
Inseminated females that did not die or were not sacrificed moribund	7	7	7	4	2	0
Females that aborted	0	1	0	0	1	0
Females not pregnant at sacrifice	1	2	2	1	1	NA
Females pregnant at sacrifice	6	4	5	3	0	NA
Corpora lutea/litter [2]	9.0 ± 4.82	7.5 ± 4.36	10.6 ± 3.78	9.3 ± 2.08	NA	NA
Implantations/litter [2]	5.8 ± 2.71	5.5 ± 2.52	4.2 ± 3.83	5.3 ± 3.21	NA	NA
Pre-implantation loss/litter [2]	3.2 ± 5.38	2.0 ± 2.16	6.4 ± 3.36	4.0 ± 2.00	NA	NA
Resorptions/litter [2]	0.3 ± 0.82	0.5 ± 0.58	0.8 ± 1.10	0.3 ± 0.58	NA	NA
Viable fetuses/litter [2]	6.6 ± 2.19	5.0 ± 2.71	3.4 ± 2.88	5.0 ± 3.46	NA	NA
Fetal weight (g) [2, 3]	46.5 ± 6.29	53.4 ± 3.98	51.1 ± 10.49	45.7 ± 4.38	NA	NA

(1) Data are numbers or averages ± SD.
(2) No statistically significant difference from controls.
(3) Litter average ± SD.
NA: Not Applicable (all animals died, were sacrificed moribund, were not pregnant, or aborted).

Adam 1992, Mercieca 1992 (main study)

In the main study, inseminated female New Zealand White rabbits were treated by gavage with propachlor (purity 96.8%) suspended in 0.5% methylcellulose in water for gd 7-19. The target doses were 0, 5, 50, or 100 mg/kg/d. Due to a dilution error during preparation, the actual doses were 0, 5.8, 58.3, or 116.7 mg/kg/d. The day of insemination was designated gd 0. There were 20 females per group. Animals that did not die, were not sacrificed moribund, and did not abort were sacrificed on gd 29. Results were reported for female survival, clinical signs, food consumption, body weight, and gross necropsy. Abortions, uterine weight, corpora lutea, implantations, resorptions, fetal death, fetal body weight, and fetal malformations were reported.

At 116.7 mg/kg/d (the high dose), two females died on gd 10. The cause of death was not determined. Females in the high dose group that died displayed reduced defecation and soft stools. One female in the control group died, apparently from gavage error. Females in the 116.7 mg/kg/d group consumed considerably less food than controls during the treatment period (approximately 41% of control, statistically significant). Food consumption in the 5.8 and 58.3 mg/kg/d groups was similar to controls. Females in the 116.7 mg/kg/d group lost weight during the dosing period (statistically significant difference from controls). Following cessation of treatment, females in the 116.7 mg/kg/d group gained more weight than the control group (statistically significant). Body weight at sacrifice was lower than controls in the 116.7 mg/kg/d group (not statistically significant). Body weight gain at sacrifice was reduced in the 116.7 mg/kg/d group (statistically significant). Body weight and weight gain during the dosing period and at sacrifice were similar in the control and the 5.8 and 58.3 mg/kg/d groups. See Table 5.

One female each in the 5.8 and 116.7 mg/kg/d groups aborted. One rabbit in the 116.7 mg/kg/d group delivered prematurely. There were no statistically significant differences between the controls and the propachlor treated groups for corpora lutea, implantation sites, or pre-implantation loss. Early resorptions were slightly higher in the 116.7 mg/kg/d group than controls (not statistically significant). There was a small, dose-related increase in late resorptions among all propachlor treated groups (not statistically significant pairwise). The number of viable fetuses per female was lower in the 116.7 mg/kg/d group than in controls (89% of controls, not statistically significant). Fetal weight was lower in the 116.7 mg/kg/d group than controls (92% of controls, not statistically significant). Results for these endpoints were similar to controls in the 5.8 and 58.3 mg/kg/d groups. See Table 6. Sporadic malformations were observed, but neither individual nor total malformations were dose-related or statistically significant. Individual variations were similar between groups, with the exception of increased frequency of bent hyoid arch in the 116.7 mg/kg/d group (statistically significant on a litter basis). The other two propachlor treated groups also had increased frequency of bent hyoid arches compared to controls, although there was not a dose-related increase (not statistically significant). See Table 7. The authors provided data indicating that the frequency of bent hyoid arch in the 116.7 mg/kg/d group was near the upper end of the historical control range.

Table 5. Selected data, main rabbit developmental study (Adam 1992, Mercieca 1992). [1]

Group (mg/kg/d)		0	5.8	58.3	116.7
Inseminated females		20	20	20	20
Females that died		1	0	0	2
Food consumption (g/animal/ day)	gd 0-7	202 ± 28.2	214 ± 19.5	206 ± 32.2	203 ± 24.9
	gd 7-10	200 ± 23.8	216 ± 20.7	195 ± 37.6	101 ± 56.1**
	gd 7-19	200 ± 24.0	219 ± 27.4	194 ± 30.4	82 ± 57.0**
	gd 19-29	170 ± 28.9	178 ± 26.4	162 ± 35.0	177 ± 30.1
	gd 0-29	190 ± 22.6	202 ± 18.3	186 ± 28.1	146 ± 28.9**
Female body weights (g)	gd 0	3350 ± 197.4	3351 ± 210.7	3375 ± 228.3	3388 ± 205.2
	gd 7	3664 ± 238.0	3720 ± 216.4	3697 ± 316.4	3688 ± 218.5
	gd 10	3694 ± 231.3	3782 ± 224.9	3752 ± 355.0	3579 ± 248.4
	gd 19	3840 ± 246.9	4009 ± 253.0	3965 ± 349.9	3374 ± 320.3**
	gd 29	4063 ± 289.0	4182 ± 277.8	4117 ± 392.9	3803 ± 279.2
	gd 29 net [2]	3649 ± 256.9	3740 ± 260.1	3672 ± 305.0	3445 ± 230.8
Female body weight change (g)	gd 0-7	313 ± 127.5	370 ± 82.8	322 ± 119.2	299 ± 94.5
	gd 7-10	30 ± 39.0	62 ± 50.0	55 ± 55.8	-108 ± 103.6**
	gd 7-19	194 ± 90.7	288 ± 102.4	268 ± 79.7	-284 ± 337.3**
	gd 19-29	223 ± 85.5	184 ± 100.7	152 ± 108.1	396 ± 152.9**
	gd 0-29	733 ± 185	838 ± 134.7	742 ± 238.5	443 ± 231.2**
	gd 0-29 net [2]	319 ± 201.5	396 ± 221.1	297 ± 191.4	85 ± 159.0**

(1) Data are numbers or averages ± SD.
(2) Body weight minus uterus weight.
NA: Not Applicable (all animals died, were sacrificed moribund, were not pregnant, or aborted).
* P<0.05 statistically significant difference from controls, Dunnett's test.
** P<0.01 statistically significant difference from controls, Dunnett's test.

Table 6. Selected data, main rabbit developmental study (Adam 1992, Mercieca 1992). [1]

Group (mg/kg/d)		0	5.8	58.3	116.7
Inseminated females that did not die		19	20	20	18
Females that aborted		0	1	0	2
Females not pregnant at sacrifice		1	2	1	1
Females pregnant at sacrifice		18	17	19	15
Females with resorptions only		0	0	1	2
Corpora lutea/litter)		9.3 ± 2.9	10.8 ± 2.7	10.0 ± 2.6	10.8 ± 2.7
Implantations/litter		6.8 ± 3.1	7.1 ± 3.4	7.4 ± 2.5	7.1 ± 2.6
Pre-implantation loss/litter		2.4 ± 1.9	3.6 ± 2.6	2.6 ± 2.5	3.7 ± 2.5
Resorptions/ litter	Early	0.4 ± 0.8	0.2 ± 0.5	0.5 ± 1.0	0.8 ± 1.2
	Late	0	0.2 ± 0.5	0.5 ± 2.3	0.6 ± 1.6
Dead fetuses/litter		0	0	0	0
Viable fetuses/litter		6.4 ± 3.1	6.8 ± 3.2	6.4 ± 3.1	5.7 ± 2.9
Fetal weight (g) [2]		47.7 ± 6.4	47.2 ± 5.0	46.6 ± 5.9	43.8 ± 5.4

(1) Data are numbers or averages ± SD. There were no statistically significant differences from controls.
(2) Litter average ± SD

Table 7. Selected data, main rabbit developmental study (Adam 1992, Mercieca 1992). (1)

Group (mg/kg/d)	0	5.8	58.3	116.7
Litters examined for malformations	18	17	18	13
Fetuses examined for malformations (includes externally, viscerally, and skeletally)	116	115	122	85
External malformations [fetuses (litters)]	0 (0)	1 (1)	2 (2)	0 (2)
Visceral malformations [fetuses (litters)]	3 (3)	2 (2)	0 (0)	0 (0)
Skeletal malformations [fetuses (litters)]	3 (2)	4 (3)	5 (4)	0 (0)
Hyoid arch(es) bent (2) [fetuses (litters)]	2 (2)	12 (6)	8 (5)	8 (6*)

(1) Data are numbers.
(2) Considered a variation by authors.
* $P < 0.05$ statistically significant difference from control group, Fisher's Exact test.

C.1.2 Developmental toxicity studies in rats

Mirkova 1975

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

Mated female white rats (strain not reported) were treated by gavage with a water suspension of Ramrod (a commercial preparation reported in this paper to be 65% propachlor) during gd 1-20. The doses were reported as 0 (control), $1/40^{th}$, $1/20^{th}$, $1/10^{th}$, and $1/5^{th}$ of the LD_{50} of Ramrod. The assumed LD_{50} was not reported. Two other papers from Bulgaria from the same time period assumed an LD_{50} of 1,200 mg/kg, based upon studies conducted for the manufacturer (Zlateva and Maleva 1979, Zlateva et al. 1979). This value is similar to the LD_{50} cited by U.S. EPA of 1,800 mg/kg (see Section B.4). If an LD_{50} of 1,200 mg/kg is assumed, the doses would have been 0, 30, 60, 120, or 240 mg/kg/d. A total of 103 females were used, but the specific group sizes were not reported. Females were sacrificed on gd 21. No maternal data were reported. Information on pre-implantation loss, post-implantation loss, total embryonal loss, fetal malformations and anomalies, fetal weight and length, and placental weight were reported.

In the $1/20^{th}$, $1/10^{th}$, and $1/5^{th}$ of LD_{50} dose groups, pre-implantation losses and total embryonal mortality were increased compared to controls (statistically significant). The magnitude of these effects was similar among these three groups, and no dose-response relationship was present. The author stated that fetal weight and cranio-caudal length were reduced in these groups compared to controls, but no numerical data were reported. The author stated that there were no differences between groups in numbers of corpora lutea, post-implantation mortality, or litter size. No numerical data for these endpoints were reported. The author stated that, at the $1/10^{th}$ and $1/5^{th}$ of LD_{50} doses, facial and cranial anomalies were observed (0.09% and 3.03%, respectively). In the $1/20^{th}$, $1/10^{th}$, and $1/5^{th}$ of LD_{50} dose groups, general fetal anomalies (e.g. hematoma) were increased (statistically significant), in a dose-related manner. Placental weights were also reduced compared to controls at these doses (statistically significant), but there was no dose-relationship. The author stated that there were no effects at $1/40^{th}$ of LD_{50} dose, but no numerical data were reported. See Table 8.

Table 8. Data from rat developmental study (Mirkova 1975). (1)

Group (fraction of LD_{50})	0	1/20	1/10	1/5
Pre-implantation loss (%)	5 ± 1%	14.5 ± 3.6%*	12.6 ± 4%*	13.7 ± 3.9%*
Total embryonal mortality (%)	9.84 ± 1.45%	21 ± 3.92%*	15.54 ± 4.5%*	15.4 ± 3.7%*
Embryos with general anomalies (e.g. hematoma) (%)	15.32%	25.2%	27.4%	39.6%
Placental weight (mg?)	531 ± 10.3	486 ± 917**	415.2 ± 14.3***	476.9 ± 11.048***

(1) Data from text. Not stated if variations are SD or SE. No numerical data for the 1/40 of LD_{50} dose were reported.
* $P < 0.05$ statistically significant difference from controls. Method not reported.
** $P < 0.01$ statistically significant difference from controls. Method not reported.
*** $P < 0.001$ statistically significant difference from controls. Method not reported.

Suba 1982 (range-finding study)

Mated female Sprague-Dawley rats were treated with propachlor (purity 96.5%) in a corn oil suspension by gavage for gd 6-19. Dose levels were 0, 100, 200, 400, 600, or 800 mg/kg/d. There were 5 females per group. Females that did not die or were not sacrificed in extremis were sacrificed on gd 20. Female mortality, body weight and weight gain, and clinical signs were reported. The numbers of copora lutea, implantations, resorptions, and live fetuses were reported. No statistical test results were reported.

All females in the three highest dose groups (400, 600, and 800 mg/kg/d) died. One female in the 200 mg/kg/d dose group died. All deaths occurred early in treatment (gd 7-12). The author stated that the cause of death for the one female that died in the 200 mg/kg/d group and three of the females that died in the 600 mg/kg/d group was gavage error. A tear in the esophagus was observed in each of these females. The cause of death for the remaining females was not determined. Some of the females that died displayed moribund appearance, inactivity, cool to touch, loss of righting reflex, dilated pupils, red material around eye, or hair loss. Loss of body weight occurred in two rats prior to death in the 400 mg/kg/d group. Lower body weight at sacrifice and lower body weight gain during treatment and during gestation was observed in the 100 and 200 mg/kg/d groups compared to controls. See Table 9.

Due to the death of all females in the groups, there were no developmental results for the 400, 600, or 800 mg/kg/d groups. Numbers of corpora lutea in the 100 and 200 mg/kg/d groups were similar to controls. Total implantations were lower and preimplantation losses higher in the 100 and 200 mg/kg/d groups than controls. Postimplantation losses in the 100 and 200 mg/kg/d groups were similar to controls. The numbers of viable fetuses per female were lower in the 100 and 200 mg/kg/d groups than controls, due to preimplantation losses. See Table 10.

Table 9. Selected data from rat range-finding developmental study (Suba 1992)

Group (mg/kg/d)		0	100	200	400	600	800
Mated females		5	5	5	5	5	5
Females died or sacrificed in extremis		0	0	1	5	5	5
Females not pregnant at sacrifice (gd 20)		1	1	2	ND	ND	ND
Females pregnant at sacrifice (gd 20)		4	4	2	ND	ND	ND
Body weight (g)	gd 0	241	229	240	242	253	237
	gd 6	264	237	261	256	278	260
	gd 9	270	243	264	222	ND	ND
	gd 20	380	321	343	ND	ND	ND
Body weight change (g)	gd 6-9	6	6	3	-34	ND	ND
	gd 6-20	116	84	82	ND	ND	ND
	gd 0-20	139	92	103	ND	ND	ND

(1) Data are numbers or averages. No indices of variation (e.g. SD) or statistical significance test results were reported. ND: No Data due to death of all females in group.

Table 10. Selected data from rat range-finding developmental study (Suba 1992)

Group (mg/kg/d)	0	100	200
Females pregnant at sacrifice (gd 20)	4	4	2
Females with total resorptions	0	1	0
Copora lutea/litter	15.0	16.3	14.0
Implantations/litter	14.8	11.8	12.0
Preimplanation loss (%) [(2)]	1.7%	8.2%	14.3%
Postimplantation loss/litter	1.3	1.0	1.0
Postimplantation loss (%) [(2)]	8.5%	8.5%	8.3%
Viable fetuses/litter	13.5	10.8	11.0

(1) Data are numbers or averages. No indices of variation (e.g. SD) or statistical significance test results were reported. No data were reported for 400, 600, or 800 mg/kg/d because all females died prior to scheduled sacrifice.
(2) Group average.

Suba 1982 (Main Study)

Mated female Sprague-Dawley rats were treated with propachlor (purity 96.5%) in a corn oil suspension by gavage for gd 6-19. Dose levels were 0, 20, 60 or 200 mg/kg/d. There were 25 females per group. Females that did not die or were not sacrificed in extremis were sacrificed on gd 20. Female mortality, body weight and weight gain, and clinical signs were reported. The numbers of copora lutea, implantations, resorptions, live fetuses, fetal weight, malformations and variations were reported.

One female in the high dose group (200 mg/kg/d) died. The author stated that this death was due to gavage error. Body weights and weight gains were similar in all groups. Excess salivation was noted in the 60 and 200 mg/kg/d groups. Dry, red matting of the eyes and nares, and lacrimation was noted in some females in the 200 mg/kg/d group. See Table 11.

The numbers of corpora lutea, implantations, resorptions, and live fetuses were similar between groups. The authors stated that fetal weights were similar between groups. However, the numerical fetal weight for the 200 mg/kg/d group was lost from the report due to poor copy quality. Small numbers of malformations and some variations were observed, with no apparent relationship to propachlor treatment. See Table 12.

Table 11. Selected data from main rat developmental study (Suba 1982). (1)

Group (mg/kg/d)		0	20	60	200
Mated females		25	25	25	25
Females died		0	0	0	1
Females not pregnant at sacrifice (gd 20)		1	1	1	0
Females pregnant at sacrifice (gd 20)		24	24	24	24
Body weight (g)	gd 0	241 ± 15.6	244 ± 17.6	242 ± 12.9	241 ± 15.0
	gd 6	269 ± 16.6	270 ± 19.6	269 ± 15.1	267 ± 17.8
	gd 9	281 ± 17.9	281 ± 21.1	280 ± 16.4	285 ± 19.2
	gd 20	388 ± 32.4	385 ± 31.8	377 ± 26.6	379 ± 24.3
	gd 20 adj. (2)	311 ± 23.1	309 ± 24.7	298 ± 20.3	298 ± 20.7
Body weight change (g)	gd 6-9	15 ± 6.7	10 ± 4.9	11 ± 4.3	8 ± 6.5
	gd 6-20	119 ± 20.8	115 ± 17.0	108 ± 18.0	111 ± 15.9
	gd 0-20	146 ± 24.4	141 ± 21.1	135 ± 20.2	137 ± 18.5
	gd 0-20 adj. (2)	69 ± 15.3	65 ± 15.7	55 ± 13.6	56 ± 14.2

(1) Data are numbers or averages SD. No statistically significant results were observed.
(2) Female body weight minus uterus weight.

Table 12. Selected data from main rat developmental study (Suba 1982). [1]

Group (mg/kg/d)	0	20	60	200
Females pregnant at sacrifice (gd 20)	24	24	24	24
Females with total resorptions	0	0	0	0
Copora lutea/litter	16.6 ± 3.16	16.5 ± 2.40	16.6 ± 2.18	17.2 ± 2.55
Implantations/litter	14.8 ± 1.54	14.2 ± 2.52	15.4 ± 1.64	15.4 ± 1.69
Preimplanation loss [4] (%)	11.5%	13.9%	7.5%	DL [3]
Postimplantation loss/litter	1.0 ± 2.22	0.7 ± 0.82	0.8 ± 0.82	0.6 ± 0.78
Postimplantation loss [4] (%)	6.5	4.7	5.4	DL [3]
Viable fetuses/litter	13.8 ± 2.77	13.5 ± 2.40	14.6 ± 2.0	14.8 ± 1.61
Fetal body weight [5] (g)	3.5 ± 0.27	3.5 ± 0.24	3.5 ± 0.7	DL [3]

(1) Data are numbers or averages SD. No statistically significant results were observed.
(2) Female body weight minus uterus weight.
(3) DL: Data Lost due to poor copy quality.
(4) Group average.
(5) Litter average.

C.2. Developmental endpoints from reproductive toxicity studies

Groya 1986

Male and female Fischer 344 rats were treated with propachlor in a two generation reproduction study with one litter in the first generation and two litters in the second generation. Animals were treated in food at concentrations calculated to yield doses of 0, 0.3, 3.0 or 30 mg/kg/d. The concentration of propachlor in the food was adjusted weekly during the premating period based upon the food consumption and body weight of the rats. During mating, pregnancy, and lactation, the females were maintained on the same concentration as the last week of the premating period. Actual propachlor concentrations in food were not reported. There were 30 animals/sex/group. F0 animals were treated for 100 days before mating, and during mating, gestation, and lactation. F1 animals were treated after weaning for 120 days before the first mating and during mating, gestation, and lactation. F1 animals were treated for one week after weaning of the first litter, and during the second mating, gestation, and lactation. Matings were one male to one female for 5 days, unless no evidence of copulation was observed, in which case the females were mated to a second male. Litters with more than 8 pups were culled to 8 pups on postnatal day (pnd) 4. Parental body weight, food consumption, clinical signs, and gross and microscopic pathology were reported. Fertility, litter size, pup weights, pup survival, and pup gross and microscopic pathology were reported.

In the F0 generation, one female in the control group died after giving birth and one female in the 3.0 mg/kg/d group died during gestation. No other adult animals died. F0 female food consumption was similar among groups during premating treatment. No food consumption data were reported for gestation or lactation. No clinical signs attributable to treatment were observed. Adult female body weights were similar among groups during premating treatment. No data were reported for gestational weights. Female body weight on pnd 1 in the 30 mg/kg/d group was slightly reduced compared to controls (statistically significant). Female body weight on pnd 28 was slightly reduced in the 0.3 mg/kg/d group compared to controls (statistically significant), but the 3.0 and 30 mg/kg/d groups were similar to controls. At sacrifice, female liver weight was higher in the 30 mg/kg/d group than controls (statistically significant for relative but not absolute weight). See Table 13. A "very slight increase in centrilobular hepatocyte eosinophilia…[and] hypertrophy" was also observed in 4 out of 10 rats from this group.

In the F1 generation, no adult females died. F1 female food consumption was generally lower in the 30 mg/kg/d group than controls during premating treatment (sometimes statistically significant). No food consumption data were reported for gestation or lactation. No clinical signs attributable to treatment were observed. F1 adult female body weights were comparable among groups during premating treatment. No data were reported for gestational weights. Female body weights were similar among groups on F1/F2a pnd 1. Female body weight on F1/F2a pnd 28 was reduced in the 0.3 mg/kg/d group compared to controls (statistically significant) but the 3.0 and 30 mg/kg/d groups were similar to controls. Female body weights were similar among groups on F1/F2b pnd 1. Female body weights on F1/F2b pnd 28 were similar among groups. At sacrifice, female liver weights were higher in the 3.0 and 30 mg/kg/d

groups than controls (statistically significant for relative but not absolute weight at 3.0, statistically significant for both at 30 mg/kg/d). See Table 13. A "very slight increase in centrilobular hepatocyte eosinophilia…[and] hypertrophy" was also observed in 7 out of 10 rats from the 30 mg/kg/d group.

In the F0/F1 litter, litter size and pup weight on pnd 1 were similar among groups. Pup survival during pnds 1-4 and 4-28 were similar among groups. Male pup body weight on pnd 28 was reduced in the 0.3 mg/kg/d group compared to controls (statistically significant). Male pup body weights on pnd 28 in the 3.0 and 30 mg/kg/d groups were similar to controls. Female pup body weights on pnd 28 were similar among groups. See Table 14. No gross external or microscopic abnormalities attributable to propachlor treatment were observed in the weanlings.

In the F1/F2a litter, litter size and pup weight on pnd 1 were similar among groups. Pup survival during pnds 1-4 and 4-28 were similar among groups. Male pup body weights on pnd 28 were similar among groups. Female pup body weight on pnd 28 was reduced in the 0.3 mg/kg/d group compared to controls. Female pup body weights on pnd 28 in the 3.0 and 30 mg/kg/d groups were similar to controls. See Table 14. No gross external or microscopic abnormalities attributable to propachlor treatment were observed in the weanlings.

In the F1/F2b litter, litter size and pup weight on pnd 1 were similar among groups. Pup survival during pnds 1-4 and 4-28 were similar among groups. Male and female pup body weights on pnd 28 were similar among groups. See Table 14. No gross external or microscopic abnormalities attributable to propachlor treatment were observed in the weanlings.

Table 13. Selected female data from rat reproductive study (Groya 1986). [1]

Group (mg/kg/d)		0	0.3	3.0	30
F0 females in study		30	30	30	30
Food consumption (g/animal/ day)	Days 1-7	12.4 ± 0.9	11.8 ± 0.7	12.2 ± 0.6	12.3 ± 0.8
	Days 99-104 [2]	12.8 ± 1.1	12.4 ± 0.9	12.7 ± 1.0	12.6 ± 1.0
F0 female body weight (g)	Day 0	100 ± 7	100 ± 4	99 ± 5	99 ± 5
	Day 105 [2]	196 ± 1	196 ± 9	193 ± 8	192 ± 10
	pnd 1	203 ± 10	198 ± 11	199 ± 8	195 ± 8*
	pnd 28	215 ± 10	207 ± 13*	213 ± 9	213 ± 12
	At sacrifice	199 ± 10	195 ± 11	196 ± 8	194 ± 10
F0 female liver weight	Absolute (g)	5.58 ± 0.43	5.46 ± 0.42	5.61 ± 0.38	5.80 ± 0.40
	Relative (g/100 g bw)	2.80 ± 0.10	2.79 ± 0.10	2.80 ± 0.17	2.99 ± 0.17*
F1 females in study		30	30	30	30
Food consumption (g/animal/ day)	Days 2-7	12.1 ± 0.6	12.0 ± 0.7	11.9 ± 0.8	11.9 ± 0.6
	Days 113-119 [2]	13.5 ± 1.0	13.3 ± 0.9	13.4 ± 1.1	13.1 ± 0.8
F1 female body weight (g)	Day 0	104 ± 10	105 ± 8	108 ± 8	102 ± 12
	Day 118 [2]	197 ± 11	192 ± 12	196 ± 10	194 ± 8
	F1/F2a pnd 1	200 ± 8	195 ± 8	196 ± 8	197 ± 9
	F1/F2a pnd 28	216 ± 11	203 ± 15*	215 ± 11	218 ± 11
	F1/F2b pnd 1	225 ± 12	219 ± 14	222 ± 12	217 ± 11
	F1/F2a pnd 28	228 ± 12	227 ± 13	234 ± 9	229 ± 11
	At sacrifice	217 ± 9	210 ± 14	216 ± 11	215 ± 11
F1 female liver weight	Absolute (g)	5.97 ± 0.41	5.91 ± 0.54	6.21 ± 0.55	6.49 ± 0.52*
	Relative (g/100 g bw)	2.75 ± 0.14	2.81 ± 0.13	2.87 ± 0.17*	3.01 ± 0.24*

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

Table 14. Selected data from rat reproductive study (Groya 1986). [1]

Group (mg/kg/d)		0	0.3	3.0	30
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 pup survival [3] (%)	pnd 1-4	99.6%	100%	99.0%	99.1%
	pnd 4-28	99.3%	100%	100%	100%
F1 pup body weight [4] (g)	pnd 1	5.9 ± 0.96	5.5 ± 0.53	5.7 ± 0.50	5.7 ± 0.52
	pnd 28 male	63 ± 7	58 ± 5*	61 ± 4	60 ± 5
	pnd 28 female	57 ± 6	54 ± 5	56 ± 4	55 ± 5
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
F2a pup survival [3] (%)	pnd 1-4	97.5%	98.7%	98.5%	99.2%
	pnd 4-28	98.8%	99.5%	98.4%	100%
F2a pup body weight [4] (g)	pnd 1	5.9 ± 0.44	5.8 ± 0.45	5.8 ± 0.58	5.8 ± 0.53
	pnd 28 male	55 ± 6	53 ± 6	55 ± 7	56 ± 6
	pnd 28 female	52 ± 5	48 ± 6*	51 ± 6	52 ± 4
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
F2b pup survival [3] (%)	pnd 1-4	98.4%	98.9%	97.1%	99.6%
	pnd 4-28	99.5%	100%	98.8%	100%
F2b pup body weight [4] (g)	pnd 1	5.7 ± 0.66	5.4 ± 0.63	5.6 ± 0.62	5.5 ± 0.43
	pnd 28 male	62 ± 6	63 ± 6	63 ± 6	61 ± 5
	pnd 28 female	57 ± 5	58 ± 4	58 ± 6	56 ± 4

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

Lemen and Thake 1995

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 groups, the initial concentration was 1,000 ppm, which was ramped up to the final concentration. The concentration in food given to the male rats was increased by 500 ppm per week, and the concentration given to female rats was increased by 1,000 ppm per week, until the target concentrations were reached on week 5. These concentrations corresponded to average doses of 0, 8.3, 80, and 400 mg/kg/d for the F0 females and 0, 7.9, and 80 mg/kg/d for the F1 females. 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 for up to 10 days, 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 female in the 1,000 ppm group died during the study. No cause of death was reported; the author considered the death to be incidental to treatment. All other F0 females survived until scheduled sacrifice. F0 females in the 5,000 ppm group had reduced food consumption compared to controls (statistically significant) during the premating, gestation, and lactation periods. Females in the 1,000 ppm group also had slightly lower food consumption than controls in most periods (occasionally statistically significant). Females in the 5,000 ppm group had reduced body weight compared to controls (statistically significant) from about the third week of treatment onwards. By the end of the premating treatment period (day 70), the 5,000 ppm group female body weight was about 86% of controls. Female body weight in the 5,000 ppm group was also reduced compared to controls (statistically significant) throughout gestation and lactation. On gd 0, female body weight in the 5,000 ppm group was about 87% of controls, and on gd 21, it was about 75% of controls. Females in the 1,000 ppm group had somewhat lower body weights than controls through most of premating, gestation and lactation (occasionally statistically significant). Absolute liver weights were comparable among the 0, 100, and 1,000 ppm groups (no organ weights were reported for the 5,000 ppm group). Relative liver weight was increased by about 6% in the 1,000 ppm group compared to controls (statistically significant). See Table 15. Also, increased incidence of centrilobular/midzonal hepatocellular hypertrophy was observed in the 1,000 ppm group compared to controls (24/30 vs. 0/30, statistically significant). No gross or microscopic pathology data were reported for the 5,000 ppm group.

As noted above, there was no adult F1 generation 5,000 ppm group. One F1 female in the control group died. No cause of death was reported; the author considered the death to be incidental to treatment. All other F1 adult females survived until scheduled sacrifice. F1 female food consumption in the 1,000 ppm group was generally lower than controls (statistically significant for the premating but not the gestation or lactation periods). Females in the 1,000 ppm group had reduced body weight compared to controls at the beginning of the premating

treatment period (statistically significant). The 1,000 ppm group body weight continued to be lower through the premating treatment period (statistically significant), and the gestation period (not statistically significant). On gd 0, female body weight in the 1,000 ppm group was about 94% of the control group, and on gd 21 it was about 95% of the control group. Female body weight in this group was reduced compared to controls on the first day of lactation (statistically significant), but only slightly lower by the end of lactation. Absolute liver weights were comparable among groups. Relative liver weight was increased by about 10% in the 1,000 ppm group compared to controls (statistically significant). See Table 16. Also, increased incidence of centrilobular/midzonal hepatocellular hypertrophy was observed in the 1,000 ppm group compared to controls (27/30 vs. 0/30, statistically significant).

F0/F1 live liter size at birth was reduced in the 5,000 ppm group compared to controls (statistically significant). There was a concentration-related upward trend of dead pups/litter at birth (not statistically significant). F1 pup survival for pnds 0-4 and 4-21 was reduced in the 5,000 ppm group compared to controls (statistically significant). Pup body weight at birth (pnd 0) was reduced in the 5,000 ppm group compared to controls (statistically significant). The 5,000 ppm group pups weighed about 87% of controls. Pups in the high concentration group grew poorly during lactation, and weighed about 31% of controls on pnd 21 (statistically significant). In the 1,000 ppm group, pup body weight on pnd 0 was somewhat lower than the control group (95% of controls, not statistically significant). Pups in the 1,000 ppm group grew more slowly and had reduced body weight compared to controls on pnd 21 (87% of controls, statistically significant). See Table 17.

The authors stated that, in the 5,000 ppm group most of the first pups weaned on pnd 21 died within one day. Numerical data (e.g. timing, numbers of pups and litters) concerning this observation were scattered and difficult to interpret in the report. Remaining females in this group were allowed to nurse until pnd 35, and switched to control (i.e. no propachlor) diet on pnd 28. After weaning, surviving pups were fed control diet for four weeks prior to sacrifice. The pups grew rapidly on control diet, but still lagged behind other groups. As mentioned above, there was no F1 5,000 ppm adult group.

F1/F2 live litter size at birth, dead pups/litter, and pnds 0-4 and 4-21 survival were similar among groups. In the 1,000 ppm group, pup body weight on pnd 0 was somewhat lower than in the control group (95% of controls, not statistically significant). Pups in the 1,000 ppm group grew more slowly and had reduced body weight compared to controls on pnd 21 (88% of controls, statistically significant). See Table 18.

Table 15. Selected data from rat reproductive study (Lemen and Thake 1995). [1]

Group (ppm)		0	100	1,000	5,000
F0 females in study		30	30	30	30
F0 female food consumption (g/animal/ day)	Days 1-8	20.6 ± 2.46	20.2 ± 2.12	17.6 ± 1.97**	17.8 ± 2.51**
	Days 14-21	22.0 ± 2.79	22.3 ± 2.55	20.5 ± 1.74	18.7 ± 3.62**
	Days 63-70 [2]	21.7 ± 2.06	21.8 ± 1.54	20.7 ± 1.56	19.2 ± 3.81**
	gd 0-7	25.6 ± 2.35	25.2 ± 2.19	24.1 ± 1.92*	18.9 ± 5.48**
	gd 7-14	24.6 ± 2.28	24.3 ± 1.90	23.8 ± 2.03	20.2 ± 4.54**
	gd 14-21	24.7 ± 2.59	24.70 ± 3.24	24.10 ± 2.86	16.6 ± 5.19**
	pnd 0-7	34.2 ± 3.60	35.6 ± 2.51	36.7 ± 2.28*	23.5 ± 5.66**
	pnd 7-14	58.6 ± 8.00	58.6 ± 5.88	57.1 ± 4.36	29.2 ± 9.29**
	pnd 14-21	71.3 ± 9.42	70.1 ± 4.77	67.9 ± 5.04*	31.3 ± 7.55**
F0 female body weight (g)	Pre-test	202.0 ± 21.58	202.5 ± 21.49	202.3 ± 21.37	202.4 ± 21.71
	Day 21	251.4 ± 24.00	248.2 ± 26.25	240.6 ± 23.50	229.3 ± 22.99**
	Day 70 [2]	306.5 ± 30.35	304.0 ± 30.22	292.1 ± 29.79	265.0 ± 26.80**
	gd 0	313.1 ± 34.45	307.5 ± 30.41	294.8 ± 30.10	273.9 ± 28.40**
	gd 21	460.6 ± 43.83	455.3 ± 39.76	444.0 ± 45.79	344.2 ± 34.75**
	pnd 0	350.4 ± 39.50	340.3 ± 35.07	322.6 ± 33.17**	251.5 ± 25.45**
	pnd 21	361.8 ± 33.69	355.6 ± 32.80	358.8 ± 31.02	259.5 ± 32.06**
F0 female liver weight	Absolute (g)	10.4 ± 1.50	10.2 ± 1.36	10.6 ± 1.33	ND
	Relative (% of bw)	3.20 ± 0.328	3.15 ± 0.261	3.39 ± 0.288*	ND

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

Table 16. Selected data from rat reproductive study (Lemen and Thake 1995). [1]

Group (ppm)		0	100	1,000
F1 females in study		30	30	30
F1 female food consumption (g/animal/ day)	Days 1-8	19.7 ± 2.18	19.2 ± 2.11	18.0 ± 1.77**
	Days 14-21	21.1 ± 2.99	19.9 ± 2.62	18.3 ± 1.67**
	Days 70-77 [2]	19.7 ± 2.33	19.1 ± 2.14	18.7 ± 1.26**
	gd 0-7	21.7 ± 1.39	21.6 ± 2.61	19.5 ± 1.88
	gd 7-14	22.8 ± 2.37	23.5 ± 3.10	21.6 ± 1.85
	gd 14-21	24.6 ± 2.69	23.6 ± 2.76	22.0 ± 1.94
	pnd 0-7	34.2 ± 5.30	32.1 ± 2.96	31.4 ± 3.87
	pnd 7-14	[3]	[3]	[3]
	pnd 14-21	69.0 ± 11.1	69.1 ± 5.79	63.2 ± 10.7
F1 female body weight (g)	Day 1	152.4 ± 27.51	146.6 ± 23.98	136.6 ± 16.21*
	Day 21	231.8 ± 29.36	222.8 ± 27.32	208.5 ± 19.58**
	Day 77 [2]	317.6 ± 41.54	303.5 ± 34.74	286.1 ± 26.31**
	gd 0	294.0 ± 37.53	298.7 ± 37.27	280.0 ± 27.15
	gd 21	428.4 ± 41.62	426.9 ± 47.32	406.3 ± 39.18
	pnd 0	337.4 ± 45.65	323.3 ± 41.12	302.1 ± 29.48**
	pnd 21	338.8 ± 38.59	337.2 ± 32.06	333.7 ± 25.23
F0 female liver weight	Absolute (g)	10.3 ± 1.27	10.0 ± 1.49	10.1 ± 1.29
	Relative (% of bw)	3.15 ± 0.425	3.24 ± 0.457	3.45 ± 0.360##

(1) Data are numbers or averages ± SD. The high concentration (5,000 ppm) group was discontinued prior to the F1 adult generation.
(2) Start of mating.
(3) Data for most females was not reported for this time period.
* $P < 0.05$ statistically significant difference from controls, Dunnett's Test.
** $P < 0.01$ statistically significant difference from controls, Dunnett's Test.
$P < 0.01$ statistically significant difference from controls, Mann-Whitney.

Table 17. Selected data from rat reproductive study (Lemen and Thake 1995). (1)

Group (ppm)		0	100	1,000	5,000
F0 females paired		30	30	30	30
Females pregnant/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
F1 Pup survival (%)	pnd 0-4	97.3 ± 6.94%	97.4 ± 3.85%	98.5 ± 3.10%	89.9 ± 12.2%##
	pnd 4-21	99.6 ± 2.36%	99.6 ± 2.32%	100 ± 0.0%	84.5 ± 33.5%#
F1 Pup weight (g)	pnd 0	6.48 ± 0.603	6.37 ± 0.619	6.18 ± 0.461	5.62 ± 0.591**
	pnd 4 (postcull)	10.2 ± 1.35	9.97 ± 1.30	9.39 ± 0.921	6.42 ± 1.35**
	pnd 21	56.7 ± 5.47	54.4 ± 4.61	49.2 ± 3.04**	17.7 ± 2.56**

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

Table 18. Selected data from rat reproductive study (Lemen and Thake 1995). (1)

Group (ppm)		0	100	1,000
F1 females paired		30	30	30
Females pregnant/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
F2 Pup survival (%)	pnd 0-4	96.5 ± 7.24%	99.2 ± 2.20%	97.0 ± 8.33%
	pnd 4-21	99.3 ± 2.95%	100 ± 0.0%	97.8 ± 11.8%
F2 Pup weight (g)	pnd 0	6.50 ± 0.670	6.37 ± 0.482	6.19 ± 0.654
	pnd 4 (postcull)	9.99 ± 1.41	10.2 ± 1.49	9.74 ± 1.56
	pnd 21	53.8 ± 7.75	51.8 ± 4.41	47.3 ± 4.81**

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

C.3. Other Relevant Data

Reduced food intake and body weight loss were observed in the high dose group of the later main rabbit developmental study (Adam 1992, Mercieca 1992). OEHHA staff have located three studies in the published literature which restricted food intake to pregnant rabbits of the same strain of (New Zealand White) and reported the developmental outcomes. In one of these studies (Clark et al. 1986), the initial maternal weights were considerably greater than the maternal weights in the propachlor study (Adam 1992, Mercieca 1992). Also, this feed restriction study did not have a true ad lib control group. However, in the other two studies (Matsuzawa et al. 1981, Petrere et al. 1993), initial maternal weights were similar to those in the propachlor study, and both had true ad lib control groups. The results of these two feed restriction studies are summarized below.

C.3.1. Rabbit Feed Restriction Studies

Matsuzawa et al. 1981

Mated female New Zealand White rabbits were fed ad lib (control) or at 150, 60, or 20 g food/animal/d for gd 6-20. The day of finding sperm in vaginal smears was designated gd 0. The initial number of rabbits was not reported; there were 6 to 10 pregnant rabbits per group. Rabbits were sacrificed on gd 29. Maternal survival, body weights, number of abortions, corpora lutea, implantations, dead embryos or fetuses, live litter size, body weight of live fetuses, external defects, and placental weights were reported.

There were no maternal deaths. The authors stated that the control rabbits consumed an average of 195-248 g/animal/d. No other data on food consumption were reported. Assuming average ad lib food consumption was around 220 g/d, food consumption for gd 6-20 in the feed restricted groups would have been 68%, 27%, and 9% of control in the 150, 60, and 20 g/d groups, respectively. Rabbits fed 150 g/d during gd 6-20 gained weight similarly to controls. Rabbits fed 60 g/d lost weight early in the feed restriction period, and average weight was roughly stable thereafter. Rabbits fed 20 g/d lost more weight during the feed restriction period than did the 60 g/d group, and also lost weight after the feed restriction period. See Table 19.

There were no abortions in the control, 150 or 60 g/d groups. In the 20 g/d group, 5 out of 6 rabbits aborted. The abortions occurred between gd 19 and 28. The percentage of dead embryos or fetuses was increased (statistically significant) in a treatment-intensity-related manner in the 60 and 20 g/d groups. The number of live fetuses per rabbit was decreased (statistically significant) in a treatment-intensity-related manner in the 60 and 20 g/d groups. Body weight of live fetuses was lower (not statistically significant) in the 60 g/d group, and substantially reduced (statistically significant) in the 20 g/d group. One external defect (umbilical hernia) was observed, in the 60 g/d group. The authors stated that this appeared to be unrelated to feeding. See Table 19.

Table 19. Selected data from rabbit feed restriction study (Matsuzawa et al. 1981). [1]

Group (g food/animal/d for gd 6-20)		Control (ad lib)	150	60	20
Females pregnant		10	7	7	6
Maternal body weight [2] (g)	gd 0	3350	3330	3300	3360
	gd 6	3460	3440	3400	3480
	gd 21	3730	3700	3290	3180
	gd 28	3900	3860	3360	3050
Maternal body weight change [3] (g)	gd 0-6	+110	+110	+100	+120
	gd 6-21	+270	+260	-110	-300
	gd 21-29	+170	+160	+70	-130
	gd 0-29	+550	+530	+60	-310
Number of abortions		0	0	0	5
Number of females with live fetuses [%]		10 [100%]	7 [100%]	7 [100%]	1 [17%]
Corpora lutea		10.2 ± 0.5	9.7 ± 1.4	8.6 ± 0.6	14
Number of implants		9.9 ± 0.5	9.1 ± 1.5	7.4 ± 0.8	11
Dead embryos or fetuses (%)		8.1	9.4	15.4*	45.5**
Number of live fetuses		9.1 ± 0.3	8.3 ± 2.0	6.3 ± 0.9*	6*
Body weight of live fetuses (g)		37.8 ± 0.8	38.5 ± 2.8	35.8 ± 1.3	23.8*
Placental weight of live fetuses (g)		4.6 ± 0.2	4.4 ± 0.4	4.8 ± 0.3	3.9*
External defects		0	0	1	0

(1) Data are numbers, averages or averages ± SE
(2) Estimated from Figure 1 (Matsuzawa et al. 1981) by OEHHA staff.
(3) Calculated from estimates from Figure 1 (Matsuzawa et al. 1981) by OEHHA staff.
* $P \leq 0.05$ statistically significant different from control (method not reported).
** $P < 0.01$ statistically significant different from control (method not reported).

Petrere et al. 1993

Artificially inseminated female New Zealand White rabbits were given food ad lib or at 150 g/d, 75 g/d, or 15 g/d for gd 6 to 18. Otherwise, all groups were given 150 g food/d. The date of insemination was designated gd 0. There were 20 females/group. Females were sacrificed on gd 30. Maternal mortality and body weight, abortions, total resorptions, corpora lutea, implantations, resorptions, dead fetuses, live litter size, fetal weight, external, visceral, and skeletal malformations and variations, and placental weight were reported.

One female in the ad lib (control) group died during the study. The cause of death was not ascertained. The authors stated that the ad lib group consumed about 220 g food/day. The authors stated that the rabbits weighed an average of 3.7 kg (range 3.0-4.5 kg) at the beginning of the experiment. No other quantitative data for body weight per se were reported. All food restricted groups had reduced weight gain compared to controls or actual weight loss during the food restriction period (gd 6-18). The effect was statistically significant and treatment intensity-related for all groups. Food restricted groups gained more weight than controls after being returned to ad lib feeding (gd 19-30) (statistically significant). See Table 20.

The percentage of females pregnant was similar between groups. There was one abortion in the control group, none in the 150 and 75 g/d groups, and three in the 15 g/d group (not statistically significant). The number of resorptions per litter was slightly elevated in the 15 g/d group compared to other groups (not statistically significant). Live litter size was slightly lower in all feed restricted groups compared to controls (not statistically significant). Fetal weights were slightly higher in the 150 g/d group than control (not statistically significant), and lower in the 15 g/d group than control (reduced about 9% in males and 12% in females). This difference was not statistically significant compared to controls, and was statistically significant compared to the 150 g/d group only for the male fetuses. See Table 20. There were no treatment intensity-related effects on external, visceral, or skeletal malformations. The percentage of litters with fetal external/visceral variations was increased in the 15 g/d group (statistically significant), although the percentage of fetuses with external/visceral variations per litter was slightly lower in this group (not SS). There were no effects on skeletal variations. The number of ossified sternebrae and other bones reported was comparable between groups. Data for unossified or partially ossified bones were not reported.

Table 20. Selected data from rabbit feed restriction study (Petrere et al. 1993). [1]

Group (g food/animal/d for gd 6-18)		Ad lib (control)	150	75	15
Females inseminated		20	20	20	20
Females dead		1	0	0	0
Maternal body weight change [2] (g)	gd 0-5	+90 ± 17	+61 ± 17	+104 ± 22	+130 ± 17#
	gd 6-18	+206 ± 25	+14 ± 29*	-203 ± 32*#	-334 ± 44*#
	gd 19-30	+152 ± 32	+312 ± 22*	+464 ± 29*#	+413 ± 58*#
Females pregnant (% of inseminated)		16 (80%)	17 (85%)	16 (80%)	18 (90%)
Abortions		1	0	0	3
Total resorptions		0	1	1	1
Viable litters at term		15	16	15	14
Corpora lutea/litter		9.7 ± 0.6	9.8 ± 0.7	10.0 ± 0.5	10.4 ± 0.9
Implantation sites/litter [3]		8.1 ± 0.8	6.2 ± 0.9	7.4 ± 0.8	8.1 ± 0.7
Preimplantation loss (%)		16.7 ± 6.3	35.5 ± 7.9	23.6 ± 5.8	18.3 ± 7.3
Live fetuses/litter		7.6 ± 0.7	6.0 ± 0.9	7.1 ± 0.8	7.4 ± 0.7
Dead fetuses/litter		0	0	0	0
Resorptions/litter [3]		0.5 ± 0.2	0.6 ± 0.2	0.7 ± 0.3	1.2 ± 0.5
Postimplantation loss [3] (%)		5.1 ± 2.1	13.2 ± 6.0	15.2 ± 7.2	14.0 ± 6.5
Fetal weight (g)	Males	54.1 ± 1.7	57.3 ± 2.6	52.4 ± 1.7	49.1 ± 2.4#
	Females	51.0 ± 1.5	52.4 ± 2.1	55.2 ± 2.1	44.8 ± 2.2

(1) Data are numbers, percentages, or averages ± SE (litter based)
(2) Estimated from Figure 1 (Petrere et al. 1993) by OEHHA staff.
(3) Includes females with total resorptions.
* $p \leq 0.0289$ significantly different from control (ad lib) by rank trend test.
# $p \leq 0.0289$ significantly different from 150 g/animal/d by rank trend test.

C.3.2. Transfer of propachlor and metabolites to milk

In the later rat reproductive study (Lemen and Thake 1995), severe adverse effects were observed in the high concentration group pups during the lactation period. Potentially, this could be due to transfer of propachlor to milk and consumption of the milk by the pups. OEHHA staff have not been able to locate any data on the transfer of propachlor to milk in rats. However, one study in milk goats did examine this transfer. Also, a study in milk cows examined the transfer of a related herbicide, alachlor.

Bakke and Price (1979)

This study examined the metabolism and excretion of propachlor in two sheep and one milk goat. Transfer to milk was examined only in the milk goat. A milking goat was treated with 1.3 mg propachlor orally (specific method not described) three times per day for 4 days. On days 5-14, the goat was treated with ^{14}C ring-labelled propachlor at the same dose and schedule. Milk was collected on days 5-14 in the morning and the evening. Urine was also collected. The goat was reported to weigh 65.2 kg. The goat was sacrificed 15 hours after the final dose.

Of the total ^{14}C radioactivity administered over 10 days, the majority was recovered in the urine, with lesser amounts in the feces and tissues, and a very small percentage (0.05%) in milk. See Table 21. The highest concentration of ^{14}C label in tissues was in the gastrointestinal tract. The authors commented that this was probably due to the fact that the last dosing was 15 hours before sacrifice. Concentrations of ^{14}C propachlor equivalent in the milk ranged from 1.9 to 4.6 ppb in the morning, and 1.6 to 8.3 ppb in the evening. For the last 5 days of treatment, the concentrations stabilized around 2 ppb in the morning and 4 ppb in the evening.

The dose of propachlor used in this study was about 0.06 mg/kg bw/d. No data on food consumption were reported. An approximation to food consumption may be calculated using the allometric regression developed by U.S. EPA (1988) for all (mammalian) species ($F = 0.065 \times W^{0.7919}$, with F in kg food, W in kg weight). This gives an approximate food intake of 1.8 kg/d. The dose used (3.9 mg/d) would be the equivalent of approximately 2.2 mg propachlor/kg food (i.e. 2.2 ppm). Using this estimate, the concentration of propachlor and its metabolites in milk were about 0.1% to 0.2% of the equivalent concentration in administered food. Thus, while propachlor and/or its metabolites were clearly transferred to milk, both the total percentage transferred and the concentration in milk were very small.

Table 21. Recovery of ^{14}C from a milk goat treated orally with ^{14}C-propachlor (Bakke and Price 1979).

Tissue/fluid/material	^{14}C recovered
Urine	73.4%
Feces	11.8%
Tissues	2.8%
Milk	0.05%
Total	88%

Lehotay and Miller 1994

This study was primarily a comparison of various immunoassays for alachlor. Alachlor is an acetanilide herbicide, with structural similarity to propachlor. Milk, urine, eggs, and liver samples were tested. One cow was given a capsule with 700 mg alachlor, reported to be a dose of 1 mg/kg. Milk and urine were collected. Alachlor was detected in milk for 4 or 5 days after dosing using the immunoassays. The immunoassays were highly specific for alachlor, with very low sensitivity for several metabolites. Quantitative results from the immunoassays were not reported. Confirmation of results was performed using Gas Chromatography/Mass Spectrometry (GC/MS). Using GC/MS, the concentrations of alachlor in milk were 78, 53, 42, and 33 ng/ml in the first 4 days. Total recovery was not reported.

This study, which used alachlor, supports the qualitative observation that propachlor is transferred to the milk. Although experimental differences preclude quantitative comparison, it appears that a relatively small percentage of alachlor was transferred.

C.4. Developmental toxicity: integrative evaluation

Data relevant to the potential developmental toxicity of propachlor are available from three rabbit and three rat developmental toxicity studies. Additionally, two rat reproductive toxicity studies also have some potentially relevant data.

In a rabbit developmental toxicity study (Schardein 1984, Keller 1987), inseminated female New Zealand White rabbits were treated with propachlor by gavage for gd 7-19 at 0, 5, 15, or 50 mg/kg/d. There were no indications of maternal toxicity in this study. Although a considerable number of females died during the study, there was no dose-response relationship and the deaths did not appear to be related to propachlor treatment. No effect on maternal body weight was observed. Pre- and post-implantation losses were higher in the 15 and 50 mg/kg/d groups than controls (not statistically significant). Live litter sizes were smaller in the 15 and 50 mg/kg/d groups than controls (statistically significant only for the 15 mg/kg/d group). Fetal weights were similar among groups. Total malformations were increased in the 15 mg/kg/d group compared to controls (statistically significant for litter but not for fetus). These mainly consisted of skeletal malformations, including costal cartilage anomaly, sternoschisis, centra anomaly, vertebral anomalies, and bent ribs. Although total and skeletal malformations were more frequent in the 50 mg/kg/d group than controls (not statistically significant), there was no dose-response relationship. The skeletal malformations observed in the 50 mg/kg/d group included centra and vertebra anomalies.

In a later range-finding study (Adam 1992, Mercieca 1992), inseminated female New Zealand White rabbits were treated with propachlor by gavage for gd 7-19 at 0, 25, 75, 125, 175, or 225 mg/kg/d. Maternal toxicity was observed in the forms of death and body weight loss or reduced body weight gain. Out of 7 females per group, mortality was 0, 0, 0, 3, 5, and 7, respectively. Body weight loss was also observed during treatment in the 75 and 125 mg/kg/d groups (statistically significant difference from controls for the 125 mg/kg/d group). No adverse developmental effects were observed in the 25, 75, or 125 mg/kg/d groups.

In the later main study (Adam 1992, Mercieca 1992), inseminated female New Zealand White rabbits were treated with propachlor by gavage for gd 7-19 at 0, 5.8, 58.3 or 116.7 mg/kg/d. Maternal toxicity was observed in the 116.7 mg/kg/d group in the forms of death (2/20), substantially reduced food consumption compared to controls (statistically significant), and body weight loss during treatment (controls gained weight: statistically significant difference). The number of early and late resorptions was higher, and the live litter size was lower in the 116.7 mg/kg/d group than controls (not statistically significant). Malformations were similar between groups. A variation, bent hyoid arch, was increased in the 116.7 mg/kg/d group (statistically significant for litter, but not fetus). Fetal weight was lower in the high dose group compared to controls (not statistically significant).

In the later rabbit developmental study (Adam 1992, Mercieca 1992), the differences in fetal outcomes between the high dose group and the control group could be due to direct effects of propachlor on the developing conceptuses or due to indirect effects including, potentially, the substantial reduction in food consumption and the weight loss observed in the pregnant females in this group. The results from this study can be compared to two feed restriction studies

(Matsuzawa et al. 1981, Petrere et al. 1993). Although these two feed restriction studies used the same strain of rabbit (New Zealand White), used similar amounts of food, and had similar initial maternal body weights, there are some notable differences in results. In the lowest food group, the maternal animals in the Matsuzawa et al. study continued to lose weight even after ad lib food was supplied (gd 21), whereas those in the Petrere et al. study gained more weight than controls. Also, the effects on dead embryos or fetuses (or resorptions and dead fetuses), live litter size, and body weight of live fetuses were substantially more pronounced in the Matsuzawa et al. study than in the Petrere et al. study. It may be more useful to compare the propachlor main rabbit study to the Petrere et al. study, since both used rabbits from the same supplier (Hazleton, Denver PA), they were conducted very close in time, and used the same numbers of females (20). In contrast, the Matsuzawa et al. study used rabbits from a different supplier (Nippon Nohsan Kogyo Company, Yokohama, Japan), was conducted about 10 years before the propachlor study, and used smaller numbers of animals.

The amount of food consumed during treatment by the propachlor high dose group (Adam 1992, Mercieca 1992) was close to but somewhat greater than the amount given to the middle food group in the Petrere et al. food restriction study (treatment period averages 82 g/animal/d vs. 75 g/animal/d, 41% vs. 34% of control). However, the loss of maternal body weight during treatment in the propachlor high dose group more closely resembled the lowest food group in the food restriction study (-284 g vs. –334 g, -8.4% vs. –9.0% of gd 0 body weights). This suggests that some toxic effect of propachlor reduced the average efficiency of food use in addition to reducing the average amount of food consumed. The propachlor high dose group had a higher number of resorptions, lower live litter size, and lower fetal weights than controls (none statistically significant). In the food restriction study middle food group, resorptions were similar to controls, live litter size was somewhat lower than controls (due mainly to pre-implantaion losses), and fetal weight was similar to controls (no statistically significant differences). In the lowest food group, resorptions were higher than controls, live litter size was very slightly lower than controls, and fetal weight was lower than controls (no statistically significant differences compared to controls).

A rat developmental toxicity study published in Bulgarian (Mirkova 1975) has been partially translated by OEHHA staff. This study was poorly reported. In this study, mated rats (strain not reported) were treated with Ramrod by gavage for gd 1-20. Ramrod was stated to be 65% propachlor. OEHHA staff has located no information on the other components of Ramrod. The doses were 0 (control), $1/40^{th}$, $1/20^{th}$, $1/10^{th}$, and $1/5^{th}$ of the assumed LD_{50}. The assumed LD_{50} was not stated. No maternal data were reported. At $1/20^{th}$, $1/10^{th}$, and $1/5^{th}$ of LD_{50}, increased pre-implantation losses and total embryonal losses were reported (statistically significant, but not dose-related). At the same doses, increased general fetal anomalies (e.g. hematoma) were observed (statistically significant and dose-related). At $1/10^{th}$ and $1/5^{th}$ of LD_{50}, increased facial and cranial anomalies were observed (dose related).

A later pair of rat developmental toxicity studies were conducted for pesticide registration purposes with relatively pure propachlor. In a range finding study (Suba 1982), mated female Sprague-Dawley rats were treated with propachlor by gavage for gd 6-19 at 0, 100, 200, 400, 600, or 800 mg/kg/d. All females in the three highest dose groups died early in the treatment period. Lower body weight gain during treatment and body weight and weight gain at sacrifice

were observed in the 100 and 200 mg/kg/d groups. Total implantations were lower, pre-implantation loss higher, and live litter size was lower in the 100 and 200 mg/kg/d groups. No statistical test results were reported.

In the main study (Suba 1982), mated female Sprague-Dawley rats were treated with propachlor by gavage for gd 6-19 at 0, 20, 60, or 200 mg/kg/d. No adverse effects on maternal body weight or weight gain were observed. No adverse developmental effects were observed.

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. There was little indication of the forms of female systemic toxicity typically observed with propachlor treatment (i.e. reduced food consumption and/or body weight). No adverse developmental effects were observed.

In a later rat reproductive 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 females, these concentrations corresponded to average doses of about 0, 8, 80, and 400 mg/kg/d. Female systemic toxicity was observed in the F0 generation in the forms of reduced food consumption and body weight in the 1,000 and 5,000 ppm groups compared to controls (often statistically significant). Similar effects were observed in the F1 generation in the 1,000 ppm group. The 5,000 ppm group was discontinued after the first generation due to severe adverse effects on pups during lactation. Live litter size and pup weight at birth in the 5,000 ppm group were reduced compared to controls (statistically significant). In the 1,000 ppm groups the live litter size was similar to controls. Pup body weight at birth was slightly lower in the 1,000 ppm groups than controls in both generations (not statistically significant).

In a study in a milk goat (Bakke and Price 1979), the pattern of rapid excretion, primarily in urine, was qualitatively similar to that observed in rats (see Section B.3). Propachlor transfer to milk was observed, but both the fraction transferred (0.05% of total dose over 10 days) and the relative concentration to equivalents in food (0.1% to 0.2%) were very small.

In summary, there have been developmental toxicity studies in rabbits and rats, and reproductive toxicity studies in rats. There were indications of developmental toxicity in the absence of maternal toxicity in an earlier rabbit study (Schardien 1984, Keller 1987). These included higher pre- and post-implantation losses, lower litter sizes, and increased malformations. Most of these 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 studies used the same strain of rabbit and higher doses. The range-finding study (Adam 1992, Mercieca 1992) found high adult mortality in the three highest dose groups. No adverse developmental effects were observed in fetuses from surviving females. The main rabbit study (Adam 1992, Mercieca 1992) used three doses up to the middle range of the pilot study, and larger numbers of animals. At the high dose, two females died, and the surviving females had substantially reduced food consumption and body weight loss during treatment. Early and late resorptions were higher, and live litter size and fetal weight were lower, in the high dose group compared to controls. These effects were not statistically significant. No increase in malformations was observed. An

increase in a variation, bent hyoid arch, was observed in the high dose group (statistically significant for litter, but not for fetus.). In a fairly comparable food restriction study (Petrere et al. 1993), the middle food group consumed similar amount of food to the high dose group in the propachlor study, but the lowest food group had similar maternal body weight changes to the high dose group in the propachlor study. The middle food group did not appear to have any effects on resorptions or fetal body weight, whereas the lowest food group had higher resorptions and lower fetal body weight. The latter changes were not statistically significant.

In an early rat developmental study published in Bulgarian (Mirkova 1975), increased pre-implantation losses and fetal anomalies were observed in rats treated with Ramrod. 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 subsequent pair of rat developmental studies were conducted using relatively pure propachlor. In the range finding study (Suba 1982), all females in the three highest dose groups died. Increased pre-implantation loss was observed in the remaining two dose groups. However, the treatment period began about the time of implantation, making interpretation difficult. In the main study (Suba 1982), conducted with larger numbers of animals, no adverse maternal or developmental effects were observed.

In the reproductive studies, no adverse developmental effects were observed in the earlier study (Groya 1986). In the later rat reproductive study (Lemen and Thake 1995), which used much higher concentrations, maternal toxicity was observed in the high concentration group in the form of reduced food consumption and body weight compared to controls (usually statistically significant). Lower maternal food consumption and body weight were also observed in the middle concentration group (occasionally statistically significant). Reduced live litter size and pup birth weight were observed in the high concentration group (statistically significant). Due to severe adverse effects on nursing pups, the high concentration group was discontinued after one generation. Lower pup birth weight was observed in the middle concentration groups compared to controls for both generations (not statistically significant).

The severe adverse effects in nursing pups in the high concentration group in the later rat reproductive study could be due to transfer of propachlor and/or its metabolites in milk. OEHHA staff have located no data on transfer of propachlor in milk of rats. Data from a single milk goat indicated that propachlor and/or its metabolites was transferred to milk, although at a very low amount and concentration compared to intake. Caution should be used in attempting to extrapolate from goat to rat, as the doses in the rat studies were much higher than in the goat, and metabolism may or may not be similar overall.

D. Female reproductive toxicity

No studies in humans providing data on the potential female reproductive toxicity of propachlor were located by OEHHA staff. Two rat reproductive toxicity studies, as well as several subchronic and chronic studies were located which provide relevant data.

D.1. Reproductive toxicity studies

Groya 1986

This study has been described above in section C.2. To briefly summarize, male and female Fischer 344 rats were treated with propachlor for two generations with one litter in the first generation and two litters in the second generation. Animals were treated in food at concentrations adjusted to yield doses of 0, 0.3, 3.0, and 30 mg/kg/d. Only slight indications of female systemic toxicity were observed (sporadic lower food consumption or body weight, increased liver weight). In the F0/F1 mating, fertility was reduced in the 3.0 mg/kg/d group compared to controls (statistically significant) but was only somewhat lower in the 30 mg/kg/d group (not statistically significant). In the F1/F2a mating, fertility was lower in the 3.0 and 30 mg/kg/d groups compared to controls (statistically significant for 3.0 mg/kg/d only). In the F1/F2b mating, fertility was comparable among groups. Litter sizes were similar between groups for all litters. No other adverse effects on female reproductive outcomes were observed. See Table 14. Weights of ovaries were not reported. Gross and microscopic examination of ovaries and other reproductive tissues found no propachlor treatment related pathology.

Lemen and Thake 1995

This study has been partially described above in section C.2. To briefly summarize, male and female Sprague-Dawley rats were treated with propachlor for two generations with one litter in each generation. Animals were treated in food at concentrations of 0, 100, 1,000 or 2,500 (male) or 5,000 (female) ppm. For the females these concentrations corresponded to doses of approximately 0, 8, 80, and 400 mg/kg/d.

Substantially reduced food consumption (statistically significant) and reduction in female body weight (statistically significant) were observed in the F0 females in the 5,000 ppm group compared to controls. Smaller reductions in food consumption (occasionally statistically significant) and body weight (sometimes statistically significant) were observed in the F0 and F1 females in the 1,000 ppm group compared to controls. See Tables 15 and 16.

For the F0 females, pre-coital length (days to mate) was similar among groups. All F0 females had confirmed copulation. F0 female fertility (percentage pregnant) was similar among groups. Gestation length was similar among groups. In the F0/F1 litter, live litter size at birth was reduced in the 5,000 ppm group compared to controls (statistically significant). Postnatal survival was also substantially reduced in the 5,000 ppm group compared to controls (statistically significant). Pup birth weight was reduced in the 5,000 ppm group compared to controls (statistically significant). Pup growth during lactation was substantially reduced in the

5,000 ppm group compared to controls (statistically significant). On pnd 21, pup weight in the 5,000 ppm group was 31% of controls. Pup weight at birth was lower in the 1,000 ppm group than controls (not statistically significant). Pup weight at weaning was reduced in the 1,000 ppm group compared to controls (statistically significant). Absolute and relative ovary weights were similar among the 0, 100, and 1,000 ppm groups (no data on ovary weights were reported for the 5,000 ppm group). See Table 22. Gross and microscopic examination of ovaries and other reproductive tissues found no propachlor treatment related effects in the 0, 100, or 1,000 ppm groups. No data on gross or microscopic pathology of ovaries or other reproductive organs were reported for the 5,000 ppm females.

As described previously, the authors stated that most of the first pups in the 5,000 ppm group to be weaned (pnd 21) died within one day. Numerical data concerning this observation were scattered and difficult to interpret in the report. The remaining F0 females were allowed to nurse until pnd 35, and switched to control (i.e. no propachlor) diet on pnd 28. Offspring were fed control diet for four weeks after weaning. Offspring grew rapidly, but continued to lag behind controls in body weight.

The authors stated that, in the F1 females, reproductive performance in the control group was unusually poor compared to historical controls. Precoital length was greater, and fertility (fraction becoming pregnant) was lower than the F0 controls. In the F1 mating, precoital length was substantially reduced in the 100 and 1,000 ppm groups compared to controls (statistically significant). All F1 females had confirmed copulation. The percentage of F1 females pregnant was increased in the 100 and 1,000 ppm groups compared to controls (statistically significant). Gestation length was reduced in the 1,000 ppm group compared to controls (statistically significant). Live litter size at birth was similar among groups, as was pup survival during lactation. Pup body weight at birth was lower in the 1,000 ppm group than controls (not statistically significant). Pup body weight at weaning was reduced in the 1,000 ppm group compared to controls (statistically significant). Absolute and relative ovary weights were similar among groups. See Table 23. Gross and microscopic examination of ovaries and other reproductive organs found no propachlor treatment related effects.

Table 22. Selected data from rat reproductive study (Lemen and Thake 1995). [1]

Group (ppm)		0	100	1,000	5,000
F0 females paired		30	30	30	30
F0 ovary weight	Absolute (g)	0.160 ± 0.0317	0.164 ± 0.0372	0.164 ± 0.0282	ND
	Relative (% of bw)	0.050 ± 0.0104	0.051 ± 0.0113	0.053 ± 0.0096	ND
Precoital length (days)		3.1 ± 3.6	3.1 ± 3.4	2.7 ± 1.6	3.2 ± 2.7
F0 females with confirmed copulation/total paired (%)		100%	100%	100%	100%
F0 females pregnant/total paired (%)		93.3%	96.7%	86.7%	86.7%
Gestation length (days)		22.5 ± 0.51	22.5 ± 0.51	22.4 ± 0.57	22.7 ± 0.55
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
F1 Pup survival pnd 0-4 (%)		97.3 ± 6.94%	97.4 ± 3.85%	98.5 ± 3.10%	89.9 ± 12.2%##
F1 Pup survival pnd 4-21 (%)		99.6 ± 2.36%	99.6 ± 2.32%	100 ± 0.0%	84.5 ± 33.5%#
F1 Pup weight (g)	pnd 0	6.48 ± 0.603	6.37 ± 0.619	6.18 ± 0.461	5.62 ± 0.591**
	pnd 4 (postcull)	10.2 ± 1.35	9.97 ± 1.30	9.39 ± 0.921	6.42 ± 1.35**
	pnd 21	56.7 ± 5.47	54.4 ± 4.61	49.2 ± 3.04**	17.7 ± 2.56**

(1) Data are numbers or averages ± SD.
ND = No Data for this group.
** $P < 0.01$ statistically significant difference from controls, Dunnett's Test.
# $P < 0.05$ statistically significant difference from controls, Mann-Whitney test.
$P < 0.01$ statistically significant difference from controls, Mann-Whitney test.

Table 23. Selected data from rat reproductive study (Lemen and Thake 1995). (1)

Group (ppm)		0	100	1,000
F1 females paired		30	30	30
F1 ovary weight	Absolute (g)	0.159 ± 0.0292	0.142 ± 0.0341	0.142 ± 0.0279
	Relative (% of bw)	0.049 ± 0.0095	0.046 ± 0.0112	0.048 ± 0.0098
Precoital length (days)		6.6 ± 5.5	2.8 ± 2.0#	3.1 ± 2.3#
F1 females with confirmed copulation/total paired (%)		100%	100%	100%
Females pregnant/paired (%)		60.0%	86.7%@	93.3%@@
Gestation length (days)		22.7 ± 0.59	22.6 ± 0.50	22.2 ± 0.43**
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
F2 Pup survival pnd 0-4 (%)		96.5 ± 7.24%	99.2 ± 2.20%	97.0 ± 8.33%
F2 Pup survival pnd 4-21 (%)		99.3 ± 2.95%	100 ± 0.0%	97.8 ± 11.8%
F2 Pup weight (g)	pnd 0	6.50 ± 0.670	6.37 ± 0.482	6.19 ± 0.654
	pnd 4 (postcull)	9.99 ± 1.41	10.2 ± 1.49	9.74 ± 1.56
	pnd 21	53.8 ± 7.75	51.8 ± 4.41	47.3 ± 4.81**

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

D.2. Subchronic and chronic studies

D.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 females, this corresponded to average doses over the 18 month study period of 0, 2.01, 10.03, or 104.89 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.

Survival of females was lower in all propachlor treated groups than in controls (statistically significant). However, there was no dose related trend, and the authors stated that the survival in the control group was unusually high (90% versus historical mean of 73%). Mean body weight gains to week 50 were reduced in the 50 ppm female group compared to controls (statistically significant), but not in the 500 ppm group. Mean body weight gains to week 78 were comparable between groups. Total food consumption was comparable between groups to weeks 50 and 78. Relative liver (with gallbladder) weights were increased in the 50 and 500 ppm groups compared to controls (statistically significant).

Weights of ovaries or other female reproductive organs were not reported. Gross and microscopic examination of ovaries and other reproductive organs found no propachlor treatment related effects.

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 females, these corresponded to average doses over the 18 month study period of 0, 19.3, 100.0, 276.7, and 1,006.9 mg/kg/d, respectively. Mice in the highest concentration group were started at 1,500 ppm and ramped up to the final concentration of 6,000 ppm. There were initially 60 animals/sex/group. Ten animals/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. Females in the 6,000 and 1,500 ppm groups had reduced food consumption compared to controls (frequently statistically significant). Females in the 6,000 ppm group had reduced body weight compared to controls after about 10 weeks of treatment (86% of controls at terminal sacrifice, statistically significant). At the interim sacrifice, females in the 1,500 and 6,000 ppm groups had increased absolute and relative liver weights compared to controls (statistically significant at 6,000 ppm). At the final sacrifice, females in the 500, 1,500, and 6,000 ppm groups had increased absolute and relative liver weights compared to controls (statistically significant). At the terminal sacrifice, females in the

6,000 ppm group had increased incidence of periportal hepatocellular hypertrophy compared to controls (statistically significant).

No data were reported on ovary weights. Gross and microscopic examination of ovaries and uteri found no propachlor related lesions.

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 females, these concentrations corresponded to average doses over the 90 day study period of 0, 140, 400, or 1,100 mg/kg/d (estimated 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. Female food consumption was reduced at 1,500 and 5,000 ppm compared to controls in the first week of the study (statistically significant). Female food consumption was reduced at 5,000 ppm compared to controls for the remainder of the study (sometimes statistically significant). Female body weights were reduced at 1,500 and 5,000 ppm compared to controls in the early part of the study (e.g. on day 30, 92% and 89% of controls, respectively) (statistically significant). Female body weights were lower at these concentrations compared to controls for the remainder of the study (sometimes statistically significant). Liver weights were increased in a concentration-related manner across all concentrations (statistically significant pairwise for absolute at 5,000 ppm and relative at 1,500 and 5,000 ppm). Incidence of centrilobular hepatocyte hypertrophy was higher in the 5,000 ppm group compared to controls (not statistically significant).

No data on ovary or other female reproductive organ weights was reported. Gross and microscopic examination of ovaries and uteri found no propachlor treatment related lesions.

D.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 females, this corresponded to average doses over the two year study period of 0, 0.60, 3.04, or 30.05 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 microscopic pathology results were reported.

Survival of females was similar among groups. Average female body weights were lower in the propachlor treated groups than controls at most time points. For the 500 ppm group, this was statistically significant at weeks, 4, 6, 12, and 14. For the 50 ppm group, this was statistically

significant at weeds 2, 4, 6, and 14. On week 14, the 500 and 50 ppm group females weighed 96% and 97% of the control group weight, respectively. Statistically significant differences in body weight were not observed at later time points. Average group food consumption varied widely from week to week. Total food consumption for weeks 1-50 and 1-104 was comparable among groups. An increase in the incidence of hepatocyte centrilobular hypertrophy at terminal sacrifice was observed in the high concentration group compared to controls (statistically significant).

Weights of ovaries or other female reproductive organs were not reported. Gross and microscopic examination of ovaries and other female reproductive organs found no propachlor treatment related effects.

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 females, these concentrations corresponded to average doses over the two year study period of 0, 6.4, 19.3, 65.5 or 292.1 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 females was similar among groups. Female food consumption in the 1,000 and 5,000 ppm groups was reduced compared to controls at most time periods (usually statistically significant). Female body weights in the 1,000 and 5,000 ppm groups were reduced compared to controls at most time periods after one month of treatment (usually statistically significant). The final body weight for females in the 5,000 ppm group was 72% of the control group body weight. There was a concentration-related increase in absolute and relative liver weights across all concentrations. Absolute liver weights at 5,000 ppm were increased compared to controls at the interim (12 month) and final sacrifices (24 month) (statistically significant). Relative liver weights at 1,500 and 5,000 ppm were increased compared to controls at the interim sacrifice (statistically significant). Relative liver weights were increased at 500, 1,500, and 5,000 ppm compared to controls at the final sacrifice (statistically significant). At the final sacrifice, the incidence of centrilobular/midzonal hepatocellular hypertrophy was increased at 500, 1,500, and 5,000 ppm compared to controls (statistically significant). In the stomach, incidence of erosion/ulceration of the pylorus and herniated mucosal glands was increased at 5,000 ppm compared to controls (statistically significant).

Weights of ovaries or other female reproductive organs were not reported. Gross and microscopic examination of ovaries and uteri found no propachlor treatment related effects.

Reyna 1984b

Male and female Sprague-Dawley rats were treated with propachlor (96.1% purity) in the diet for up to three months. The target concentrations were 0, 300, 1,500, and 7,500 ppm. In females these concentrations corresponded to average doses over the three month study period of 0, 24, 120, or 540 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. Female food consumption for the first week of treatment was reduced at 1,500 ppm compared to controls (statistically significant). Female food consumption on a g food/kg body weight basis was reduced through week 5 of treatment at 7,500 ppm compared to controls (statistically significant). Female body weight was reduced at 1,500 and 7,500 ppm compared to controls (93% and 64% of controls at end of treatment, respectively, statistically significant). Several female absolute organ weights were reduced, but relative organ weights were increased at 7,500 ppm compared to controls (some statistically significant). However, female absolute liver weights were similar among groups. Female relative liver weights were increased at 1,500 and 7,500 ppm compared to controls (statistically significant).

No data on ovary or other female reproductive organ weights were reported. Gross and microscopic examinations of ovaries or uteri found no propachlor treatment related effects.

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 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. Female food consumption was reduced in the 500 mg/kg/d group compared to controls for weeks two and three (statistically significant for week three). Female food consumption was reduced in the 150 mg/kg/d group compared to controls for week three (statistically significant). A dose-related lowering of female body weight was observed by the end of the study across all doses (not statistically significant pairwise). Female body weight gain was reduced at 500 mg/kg/d compared to controls for weeks one and two (statistically significant for week one). Female body weight gain was reduced at 150 mg/kg/d compared to controls for week three (statistically significant). Female liver weights were similar among groups. See Table 24. Microscopic examination of the livers of 500 mg/kg/d and control groups found no propachlor treatment related effects.

Ovary weights were similar among groups. See Table 24. No gross lesions of the ovaries were observed. Microscopic examination of the ovaries was not performed.

Table 24. Selected female data from rat dermal study (Rush 1998). (1)

Group (mg/kg/d)		0	40	150	500
Number of females		10	10	10	10
Female food consumption (g/animal/d)	Days 1-8	22 ± 1.8	23 ± 1.0	22 ± 1.7	21 ± 1.2
	Days 8-15	25 ± 2.6	24 ± 1.7	24 ± 2.1	22 ± 1.4
	Days 15-21	24 ± 2.3	23 ± 1.6	22 ± 1.3*	22 ± 1.2*
Female body weight (g)	Day –1	166 ± 9.0	167 ± 8.5	166 ± 7.2	166 ± 7.5
	Day 8	203 ± 15.7	202 ± 9.8	200 ± 12.2	194 ± 9.4
	Day 15	227 ± 23.3	226 ± 15.4	223 ± 13.3	213 ± 11.2
	Day 21	239 ± 26.1	236 ± 15.7	226 ± 14.2	225 ± 10.4
Female body weight gain (g)	Days –1-8	37 ± 8.0	35 ± 4.5	34 ± 7.9	28 ± 7.6*
	Days 8-15	23 ± 8.7	24 ± 9.4	23 ± 4.4	19 ± 5.4
	Days 15-21	12 ± 5.9	11 ± 6.9	3 ± 6.7*	12 ± 7.3
Female liver weight	Absolute (g)	8.11 ± 0.980	8.24 ± 0.961	7.93 ± 0.870	7.98 ± 0.607
	Relative (% of bw)	3.87 ± 0.162	3.90 ± 0.317	3.88 ± 0.264	3.96 ± 0.204
Ovary weight	Absolute (g)	0.0957 ± 0.00778	0.0983 ± 0.02206	0.0934 ± 0.01627	0.0887 ± 0.01342
	Relative (% of bw)	0.0458 ± 0.00284	0.0464 ± 0.00880	0.0456 ± 0.00645	0.0440 ± 0.00615

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

D.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 average doses over the 90 day study period of 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 females, reduced food consumption and body weight gain in all propachlor treated groups compared to controls were observed. These observations were especially evident in the high concentration group. See Table 25.

Ovary weights varied considerably between groups. However, there were no statistically significant differences between groups nor was there a concentration-related trend. See Table 25. Ovaries were examined for gross and microscopic pathology. No lesions were observed.

Table 25. Selected female data from dog subchronic study (Naylor and Ruecker 1985).

Group (ppm)		0	100	500	1,500
Number of females		6	6	6	6
Female food consumption (g/animal/d) (1)	Days 1-7	318.4	287.4	246.0	204.9
	Days 14-21	339.5	301.7	297.7	185.9
	Days 49-56	369.9	360.4	335.0	241.9
	Days 84-91	373.0	312.4	329.8	266.6
	Average: days 1-91	345.8	329.5	312.9	231.7
Female body weight (kg) (2)	Day 0	7.3 ± 0.59	7.3 ± 0.65	7.2 ± 0.93	7.5 ± 0.79
	Day 21	7.8 ± 0.78	7.7 ± 0.80	7.1 ± 1.07	7.0 ± 1.01
	Day 56	8.1 ± 1.23	8.0 ± 1.03	7.2 ± 1.10	7.3 ± 0.92
	Day 91	8.5 ± 1.42	8.3 ± 1.26	7.4 ± 1.16	7.7 ± 0.84
Female body weight gain (%) (1)		14.9%	12.2%	1.4%	1.3%
Ovary weight (3)	Absolute (g)	0.943 ± 0.211	1.053 ± 0.168	1.484 ± 0.491	1.143 ± 0.206
	Relative (g/100 g bw)	0.011 ± 0.002	0.013 ± 0.002	0.019 ± 0.006	0.014 ± 0.002

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

Naylor and Ruecker 1986

Male and female beagle dogs were treated with propachlor (97.1% purity) in feed for one year. Animals were about six months of age at the beginning of the study. Nominal concentrations were 0, 25, 250, or 1,000 ppm. In females, this corresponded to average doses over the one year study period of 0, 0.9, 8.9, and 32.8 mg/kg/d, respectively. Animals in the nominal 250 ppm group were ramped up from 25 ppm in two steps over 8 days. Animals in the nominal 1,000 ppm group were ramped up from 25 ppm in five steps 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 females, food intake was lower in the high concentration group than in controls (not statistically significant). The authors attributed this to poor feed palatability at the high propachlor concentration. In the high concentration group, females gained less weight initially, and remained at lower weights throughout the study compared to controls (final weight 92% of controls) (not statistically significant). See Table 26.

Ovary weights varied considerably between groups. However, there were no statistically significant differences between groups nor was there a concentration-related trend. Estrus was observed more frequently in the propachlor treated groups than controls. The authors did not discuss these observations in the report. See Table 26. Gross and microscopic examination of ovaries found no lesions.

Table 26. Selected female data from dog chronic study (Naylor and Ruecker 1986).

Group (ppm)		0	25	250	1,000
Number of females		6	6	6	6
Female food consumption (g/animal/ day) [(1)]	Days 1-8	233.1	249.4	224.6	274.0
	Days 22-29	284.3	294.6	284.4	208.5
	Days 78-86	286.1	271.0	293.2	236.7
	Days 162-170	321.8	282.1	280.6	262.4
	Days 379-386	321.2	298.4	303.6	242.3
Female body weight (kg) [(2)]	Day 0	6.7 ± 0.44	6.6 ± 0.56	6.8 ± 0.83	6.6 ± 0.44
	Day 29	7.2 ± 0.26	7.0 ± 0.86	7.3 ± 0.62	6.8 ± 0.79
	Day 86	8.0 ± 0.34	7.9 ± 0.89	8.1 ± 0.66	7.2 ± 0.86
	Day 170	8.2 ± 0.24	8.4 ± 0.90	8.2 ± 0.73	7.6 ± 1.00
	Day 386	8.9 ± 0.69	9.1 ± 1.12	9.2 ± 0.76	8.2 ± 1.22
Ovary weight at sacrifice [(3)]	Absolute (g)	1.150 ± 0.146	0.982 ± 0.088	1.318 ± 0.186	0.861 ± 0.199
	Relative (g/100 g bw)	0.013 ± 0.002	0.011 ± 0.001	0.016 ± 0.002	0.010 ± 0.002
Estrus [number of occurances (number of animals)] [(4)]		1 (1)	7 (4)	8 (6)	11 (5)

(1) Average (indices variation, e.g. SD, not reported). No statistically significant differences were found. Dunnett's test.
(2) Average ± SD. No statistically significant differences were found. Dunnett's test.
(3) Average ± SE. No statistically significant differences were found. ANOVA and Dunnett's test.
(4) Not clear if a statistical significance test was performed.

D.3. Female Reproductive Toxicity: Integrative Evaluation

Data relevant to the potential female reproductive toxicity of propachlor are available from two rat reproductive toxicity studies. 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. There was little indication of the forms of female systemic toxicity typically observed with propachlor treatment (i.e. reduced food consumption and/or body weight). 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/d concentration groups 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 and survival during lactation were similar among groups, as were pup body weights at birth and weaning.

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 females, these concentrations corresponded to average doses of about 0, 8, 80, and 400 mg/kg/d. Female systemic toxicity was observed in the F0 generation in the forms of reduced food consumption and body weight in the 1,000 and 5,000 ppm groups compared to controls (often statistically significant). Similar effects were observed in the F1 generation in the 1,000 ppm group. The 5,000 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 females copulating, fertility (percentage of females pregnant), or gestation length. In the F0/F1 litter, live litter size and pup weight at birth were reduced in the 5,000 ppm group compared to controls (statistically significant). These pups also had reduced survival and weight gain during lactation compared to controls. On pnd 21, the 5,000 ppm group pup body weight was about 31% of controls. In both litters, pup body weight at birth was slightly lower in the 1,000 ppm groups than controls (not statistically significant). In both litters, pup body weight at weaning was reduced in the 1,000 ppm group compared to controls (statistically significant).

The adverse effects on pups during lactation in the above rat study could have been due to transfer of propachlor to milk. As summarized in section C.3.2, no data on transfer of propachlor to milk in rats was located. A study of propachlor in a milk goat observed transfer of orally administered propachlor to milk. However, both the percentage transferred and the concentration in milk relative to equivalent concentration in feed were very low.

Some studies have examined the effects of propachlor treatment on ovary weight. These include studies in rats and dogs. No propachlor treatment related adverse effects were observed.

Several studies have reported on gross and/or microscopic examination of ovaries and sometimes other female reproductive organs. These include studies in mice, rats, and dogs. No propachlor treatment related adverse effects were 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 high concentration group had reduced live litter size at birth, reduced birth weight, reduced pup survival during lactation, and severely reduced pup body weight gain during lactation. The high concentration group was discontinued after the first generation. The middle concentration group had slightly lower pup body weight at birth than controls, and reduced pup weight at weaning for both generations.

In the later rat reproductive study, the effects on litter size at birth and birth weight at the high concentration, and body weight at birth at the middle concentration, could be ascribed to either developmental toxicity or to female reproductive toxicity. The same is the case for the reduced survival during lactation and pup weight at weaning at the high concentration, and reduced pup weight at weaning at the middle concentration. The adverse effects observed in nursing pups could be due to transfer of propachlor in milk. However, a study in a milk goat found very little transfer of propachlor in milk. Extrapolation of this observation to rats is problematic, due to much higher doses in rats, and possible differences in metabolism. Another possibility is that the effects observed during lactation were due to impaired milk production. OEHHA staff have not located any relevant information on this possibility.

E. Male Reproductive Toxicity

No studies in humans providing data on the potential male reproductive toxicity of propachlor were located by OEHHA staff. Two rat reproductive toxicity studies, a rat dominant lethal study, as well as several subchronic and chronic studies were located which provide relevant data.

E.1. Reproductive toxicity studies

Groya 1986

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 Fischer 344 rats were treated with propachlor in a two generation reproduction study with one litter in the first generation and two litters in the second generation. Animals were treated in food at concentrations calculated to yield doses of 0, 0.3, 3.0 or 30 mg/kg/d. There were 30 animals/sex/group. F0 animals were treated for 100 days before mating, and during mating, gestation, and lactation. F1 animals were treated after weaning for 120 days before the first mating and during mating, gestation, and lactation. F1 animals were treated for one week after weaning of the first litter, and during the second mating, gestation, and lactation. Matings were one male to one female, unless no evidence of copulation was observed, in which case the females were mated to a second male. Litters with more than 8 pups were culled to 8 pups on postnatal day (pnd) 4. Parental body weight, food consumption, clinical signs, and gross and microscopic pathology were reported. Fertility, litter size, pup weights, pup survival, and pup gross and microscopic pathology were reported.

In the F0 generation, no adult males died. F0 male food consumption was similar among groups during premating treatment. F0 adult male body weights on premating day 0 (i.e. before the beginning of propachlor treatment) were reduced at 30 mg/kg/d compared to controls (statistically significant). Male body weights in the 30 mg/kg/d group continued to be somewhat lower than controls throughout the treatment period (not statistically significant). At sacrifice, male liver weight was higher in the 30 mg/kg/d group than controls (statistically significant for relative but not absolute weight). See Table 27. Gross and microscopic examination found no effects on liver attributable to propachlor treatment.

In the F1 generation, no adult males died. F1 male food consumption was reduced during the premating period in the 30 mg/kg/d group compared to controls (sometimes statistically significant). F1 male body weights were reduced at 30 mg/kg/d compared to controls (statistically significant from treatment day 20 onwards). At sacrifice, male absolute liver weights were similar among groups, but relative liver weights were increased in the 3.0 and 30 mg/kg/d groups compared to controls (statistically significant). See Table 27. Gross and microscopic examination found no effects on liver attributable to propachlor treatment.

In the F0 males, absolute and relative testes weights were similar among groups. In the F1 males, absolute testes weights were slightly higher in all propachlor treated groups than in controls (not statistically significant). Relative testes weight were increased compared to

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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