



Cornell University
*Program on Breast Cancer and Environmental
Risk Factors in New York State (BCERF)**

Critical Evaluation # 9
October, 1999

**Critical Evaluation of Chlorpyrifos'
Breast Cancer Risk**

by

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Supported by grants from:
New York State Dept. of Health
USDA-Regional NYC174423

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Critical Evaluation of Chlorpyrifos' Breast Cancer Risk

Author's Note: The reader is encouraged to read the attached document, Appendix B, which includes an explanation of the BCERF Breast Cancer Risk Classification System, before reading this Critical Evaluation.

Introduction:

Chlorpyrifos is an extensively used insecticide in agricultural and non-agricultural settings (Racke, 1993). It is used in the two major industries in New York State, dairy and orchard (NASS, 1995). It has been found in the air and dust in homes, indicating the potential for non-occupational exposure (Gurunathan et al., 1998). There have been some reports of chlorpyrifos residues in food (MacIntosh et al., 1996). There have been many cases of accidental poisoning with this chemical (Maddy and Edmiston, 1988).

While there have been many studies and reviews of the toxicological effects of chlorpyrifos, especially its neurotoxic effects (ATSDR, 1997), its cancer-causing potential has not been well studied. This chemical has been selected for an evaluation based on its increasing use, the high potential for non-occupational exposure and the lack of a cancer-based classification by EPA, NTP or IARC (ATSDR, 1997).

I. Chemical Information

A. Common Names: Chlorpyrifos, chlorpyriphos, chlorpyriphos-ethyl (Worthing, 1991).

B. Chemical Name: O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) phosphorothioate (Worthing, 1991).

C. Chemical Formula: C₉H₁₁Cl₃NO₃PS (Worthing, 1991)

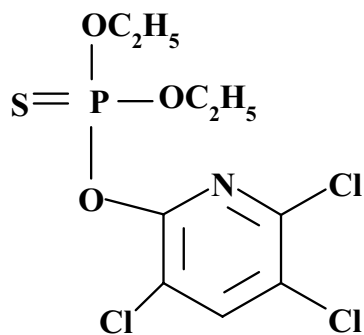
D. Formulators' Trade Names*: Aciban® (Agro Chemicals Industries Ltd.); Chlorofos® (Agrochemicals Industries Co. Ltd.); Amichlor® (Agrolex Pte. Tld.); Chlorver® (Agroquimicos Versa, S.A. de C.V.); Agrosban® (AGRO-SAN Kimya Sanayi ve Ticaret A.S.); Pyrimobeed® (Arab Pesticide Industries Co.-Mobeed); Deviban® (Devidayal Pvt. Ltd.); Dhanvan® (Dhanuka Pesticides Ltd.); Piridane® (Diachem S.p.A.); Pyrinox® (Dupocsa); Trishul® (E.I.D. Parry (India) Ltd.); Chlorfos® (Griffin Corp.); Lorsban® 50-W (Gowan Co.); Lorsban® 30, Lorsban® 50-SL (Gustafson, Inc.); Priiban® (Hektas Ticaret T.A.S.); Dursban® (Hui Kwang Chemical Co., Ltd.); Blaze® (Indofil Chemicals Co.); Knocker® (Ingenieria Industrial, S.A. de C.V.); Pirifos® (Insecticidas Internacionales, C.A.); RIMI 101® (Jewnlin-Joffe Industry Ltd.); Korban® (Koruma Tarim A.S.); Cugat® (Lainco, S.A.); Classic® 20 (Lupin Agrochemicals (I) Ltd.); Terpan® (Midiltipi Agro-Chemicals, Inc.); Colonel® (Paushak Ltd.); Duropaz® (Pazchem

Ltd.); Brodan® (Planters Products); Chloreph® (Reposo S.A.I.C.); Woproban® (B.V. Industrie-Handelsonderneming Simonis); Robon® (Sree Ramcides Chemicals Pvt. Ltd.); Chlorofet® (VAPCO); PT® 1325 ME DuraGuard® (Whitmire Micro-Gen Research Laboratories); Eradex® (Meister, 1998).

E. Trade Mixes*: Dimeclor® (+ Dimethoate), Smash® (+ methomyl) (Agrides, S.A.); Acifaz® (+ cypermethrin) (Agro Chemicals Industries Ltd.); Araoil® (+ oil); Piritan® (+ dimethoate) (Aragonesas Agro S. A.); Salut®, Saluthion® (+ dimethoate) (BASF AG); Chlorcyrin® (+ cypermethrin); Chlormezyl® (+ dimethoate), Diafos® (+ diazinon) (Chimac-Agriphar S. A.); Ebon® (+ cypermethrin), Scorpoton® (+ diazinon), Damfox®, Lantos® (+ dimethoate), Micekill® (+ fenitrothion), Malasol® (+ malathion) 9Helb USA, Inc.); Torpedo® (+ cypermethrin) (Insecticidea Internacionales, C.A.); Clatar® (+ phosmet) (Lainco, S.A.); Polirac® (+ endosulfan) (Luxan B.V.); Dorsan-C® (+ cypermethrin) (Luxemborg Industries (Pamol) Ltd.); Cypadur® (+ cypermethrin) (Pazchem Ltd.) (Meister, 1998).

F. CAS Registry Number: 2921-88-2

G. Chemical Structure:



H. Major Metabolites: Chlorpyrifos is rapidly degraded in the environment. Its hydrolysis and photolysis produces 3,5,6-trichloro-2-pyridinol (TCP) and diethyl thiophosphate (Montgomery, 1993). Other products of chlorpyrifos hydrolysis are O-ethyl O-hydrogen-O-(3,5,6-trichloro-2-pyridyl) phosphorothioate, and O,O-dihydrogen-O-(3,5,6-trichloro-2-pyridyl) phosphorothioate (Montgomery, 1993).

* Trade names are used herein for convenience and informational purposes only. No endorsements of products is intended and no criticism of unnamed products is implied.

The major metabolites found in the serum and urine of chlorpyrifos poisoned humans were TCP, diethylphosphate and diethylphosphorothioate. Chlorpyrifos-oxon was not detected (Drevenkar et al., 1993). TCP levels in the urine have been used to monitor chlorpyrifos exposure in humans (Hill et al., 1995). While diethyl phosphate levels in the urine have also been used in some studies (Hayes et al., 1980), these metabolites are common to all organophosphates and not specific to chlorpyrifos. Excretion and metabolism patterns observed for chlorpyrifos in mammals have been similar. More than 90% of absorbed chlorpyrifos was found to be eliminated in the urine in animal studies (Smith et al., 1966). In rats, the major metabolites identified were 3,5,6-trichloro-2-pyridinal phosphate, TCP and O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate (See Section VI. C.).

II. History of Use and Usage

A. History of Use and Nomenclature:

Chlorpyrifos, or O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) phosphorothioate, belongs to the family of organophosphate pesticides (OP). Its insecticidal properties were first reported in 1965, and it was commercially introduced as a pesticide by Dow Chemical Co. the same year (Worthing, 1991). Chlorpyrifos has contact toxicity against a broad range of insects as well as spiders, mites and ticks. It is also effective as a stomach poison and a fumigant (Racke, 1993).

B. Usage:

Since its introduction in the mid-1960s, chlorpyrifos has been used as a broad-spectrum insecticide in agricultural and non-agricultural settings. In non-agricultural settings, it is used in many different indoor areas such as homes, offices, schools, hotels, hospitals and restaurants (ATSDR, 1997). It is used outdoors to control insects in turfgrass, ornamental plants and shrubs. Chlorpyrifos is used to protect foundations of homes against fire ants and termites. Chlorpyrifos was first registered as a termiticide in the US in 1980 (Racke, 1993). The annual termite control use of chlorpyrifos is estimated at 1.7 million pounds (lbs) of active ingredient (AI) (ATSDR, 1997). Chlorpyrifos has replaced chlordane and heptachlor in termiticidal treatments of crawl-spaces, cracks and crevices (Wright et al., 1991). The diverse residential use of chlorpyrifos included widespread indoor use as sprays on carpets and floors against fleas, crack and crevice applications against cockroaches and ants, in ant-traps, for the protection of wood in pressure-treated wood and in foundations against termites (Racke, 1993). Chlorpyrifos was used to spray entire carpeted areas against fleas and ticks, and to spray pets. These uses will be discontinued. It will still be used for spot treatments in homes (cracks and crevices), in ant-traps and in flea collars for pets (EPA, 1997).

Chlorpyrifos use in agriculture was introduced in the mid-1970s. It has been used as a foliar insecticide (treatment of leaves) for alfalfa and cotton crops to protect against aphids, armyworms, pillbugs, chinch bugs, common stalk borer, corn borers, corn earworm, corn rootworm adults, cutworms, flea beetle adults, grasshoppers and the lesser cornstalk borer. Chlorpyrifos is also used as a soil insecticide for corn and peanut fields. It is used for seed treatments of corn and to protect stored grain and other products from insects (Meister, 1998; Racke, 1993). Chlorpyrifos is used to spray fruit trees in orchards against aphids, cutworms, flies and borers (Racke, 1993). Chlorpyrifos is still used in animal farms, but its use in spray-on and pour-on applications for cattle and sheep is no longer available (Racke, 1993).

The agricultural use of chlorpyrifos has doubled since the 1980s. Agricultural use during the years 1990 to 1993 was estimated to be 14.8 million lbs AI per year (Gianessi and Anderson, 1995a). Chlorpyrifos ranked as the tenth most used insecticide in agriculture during that period. It is estimated that 218.6 thousand lbs of chlorpyrifos AI was applied for agriculture use annually in New York State during the same time period, making it the eighth most used insecticide on cropland in the state (Gianessi and Anderson, 1995b).

The US Environmental Protection Agency (EPA) has estimated that 9 to 13 million lbs AI chlorpyrifos was used in the production of agricultural crops nationwide in 1995. This amount is lower than the estimated use in 1993 of 10 to 15 million lbs AI, but higher than the estimated use in 1987 of 6 to 9 million lbs AI (Aspelin, 1997). The most recent estimates of annual home and garden use of chlorpyrifos is two to four million lbs (Aspelin, 1997). Industrial and commercial application of chlorpyrifos was estimated to be 9 to 13 million lbs AI annually during 1994 to 1995 (Aspelin, 1997). By these estimates, the non-agricultural use of chlorpyrifos in 1995 was as high or higher than its agricultural use.

Of the total chlorpyrifos used in the US, 57% is applied to corn and 5 to 6% to cotton. Commercial pest control applications, lawn and garden treatments account for 20 to 22% of its use. The remaining 9 to 13% is used in domestic dwellings and on residential lawns and gardens (Cantilli, 1991).

III. Current Regulatory Status:

A. Regulatory Status:

Chlorpyrifos is regulated under the Emergency Planning and Community Right-to-Know Act of 1986. Under this act, the annual release of this chemical into the environment needs to be reported by all operators of facilities that manufacture, import, process or

otherwise use this chemical (ATSDR, 1997). Labels of chlorpyrifos containing products need to carry the signal words “caution” or “warning” (Meister, 1998).

The principal manufacturer and registrant of chlorpyrifos, DowElanco and EPA reached an agreement in January 1997 on ways to reduce the risk of residential exposure. According to this agreement, all residential total-release foggers, broadcast uses of chlorpyrifos, direct application products for pets such as sprays, shampoos and dips, will be canceled. Further, the labels on chlorpyrifos will be revised to prohibit the use of the pesticide in inappropriate areas which could lead to its accumulation on toys, drapes, furniture, etc. (EPA, 1997). These changes were expected to take effect in 1998. Indoor residential uses that would continue are crack and crevice applications, and use in pet collars.

B. Clean Water Act Requirements:

Chlorpyrifos is designated as a hazardous substance and EPA requires that discharges of more than one lb of chlorpyrifos into the environment be reported (ATSDR, 1997). There has been no maximum contaminant level (MCL) set for its presence in public drinking water supplies. However, health advisory levels (HAs) have been set:

Health Advisory:

10 kg child

One day = 0.03 mg/L

Ten day = 0.03 mg/L

70 kg adult

Long term = 0.1 mg/L

Lifetime = 0.02 mg/L

The HAs are non-enforceable limits of the concentration of the chemical in the drinking water that is not expected to cause any adverse noncarcinogenic health effects when consumed for no more than the time period specified, with a margin of safety (USEPA, 1996).

C. Workplace Regulations:

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Threshold Limit Value (TLV)-Time Weighted Average of 0.2 mg/m³ and a short-term exposure limit of 0.6 mg/m³ for dermal exposures (Cantilli, 1991).

D. Food Tolerances:

EPA sets the maximum amount of a pesticide that is permitted to occur on the edible portion of raw agricultural commodities and in processed foods, called tolerances. Residue tolerances for chlorpyrifos and its metabolite, TCP are: 1 to 2 parts per million

(ppm) in fruits; 0.1 ppm in mushrooms and seed and pod vegetables; 2 ppm in leafy vegetables; 0.5 ppm in tomatoes (USEPA, 1998). Based on the absence of decreased plasma cholinesterase in adult male human volunteers exposed to chlorpyrifos orally for 21 days, a no-observed-adverse-effect level (NOAEL) was set at 0.03 mg/kg/day. An oral reference dose (RfD) of 0.003 mg/kg/day was derived for chlorpyrifos from the NOAEL, by applying an uncertainty factor of 10 (Cantilli, 1991).

IV. Summary of Evidence of Overall Carcinogenicity (Non-Breast Sites)

A. Human Studies

1. Case Reports:

Case-reports of exposure and subsequent diagnosis of cancer are not sufficient evidence to establish a cause and effect relationship. However, case-reports can serve as useful indicators for an association that needs to be followed in large epidemiological studies.

There are many case-reports documenting clinical symptoms following acute exposure to chlorpyrifos (Hodgson et al., 1986; Maddy and Edmiston, 1988; Rosenberg and Quenon, 1988; Sesline et al., 1994; Shemesh et al., 1988). Chlorpyrifos causes plasma cholinesterases inhibition, which serves as a biomarker for exposure. The toxicological significance of this inhibition are controversial (Cochran et al., 1995). While the inhibition of cholinesterases and clinical symptoms associated with chlorpyrifos poisoning have been documented, none of the case-reports have reported on cancer incidence following chlorpyrifos exposures.

2. Population-Based Case-Control Studies:

A case-control study has evaluated pesticide exposure and the incidence of non-Hodgkin's lymphoma (NHL) in women agricultural workers (119 cases, 471 controls) from eastern Nebraska (Zahm and Babitt, 1993). The odds ratio (OR) for NHL was significantly increased in the six cases in this study who had personally handled OPs (OR = 4.5; 95% CI 1.1 to 17.9). Only one case had reported handling chlorpyrifos specifically. The very small numbers of women exposed to OP, makes any conclusions on the role of OP in NHL etiology unclear. Larger epidemiological studies are needed to evaluate any association of cancer and exposure to chlorpyrifos.

3. Cohort Studies:

A cohort of 696 California pet handlers was surveyed for exposure to flea control products and any health symptoms (Ames et al., 1989). While symptoms of skin, eye and respiratory illnesses were reported in association with exposure to flea products, this study did not evaluate cancer incidences.

The Dow Chemical Co. has been the principal manufacturer of chlorpyrifos since 1969. It has conducted a study on the cause of morbidity of 175 employees potentially exposed to chlorpyrifos and 335 controls matched for age, sex, race, year and status of hire (hourly or salary). Diseases diagnosed between 1977 and 1985 were recorded in the company's medical records. These records were abstracted and coded according to the international classification of diseases. A mortality study was done to compare the incidence of diseases of the nervous system, the respiratory system and ill defined conditions among the cohort of workers who had the potential for exposure to chlorpyrifos with other workers who had no exposure. In the abstraction of information from the company's medical records, diseases diagnosed were grouped by the affected organ, but cancer incidence was not specified. Only diseases that occurred during the period of exposure or within one month of leaving the job were included, thus restricting the analysis to the acute effects of chlorpyrifos. Further, any conditions that were treated by an external physician (not the company's medical system) were not recorded. The small sample size and the short period covered by this study were other limiting factors (Bremmer et al., 1988). An update to this study included 496 employees at Dow Chemical Co. (423 male, 73 female) potentially exposed to chlorpyrifos, and 911 controls matched for age, race, sex, pay and year of hire (Braun et al., 1981). Due to the limitations listed above, neither the original mortality study or its update can be used to assess whether or not chlorpyrifos caused an increase in cancer-related mortality.

4. Summary, Human Studies:

Case-reports of chlorpyrifos-caused health effects have not reported cancer in association with its exposure. Epidemiological studies done so far have either had very few cases of exposure to chlorpyrifos (Zahm and Babitt, 1993), or have not provided reports on cancer incidences (Braun et al., 1981; Bremmer et al., 1988). Thus, there is no evidence that allows the evaluation of the carcinogenic potential of chlorpyrifos in humans. Chlorpyrifos is a widely used insecticide and further studies on occupationally exposed populations are needed to determine if it has the potential to affect cancer risk.

B. Experimental Animal Studies:

The cholinesterase inhibition effect of chlorpyrifos has been well documented in many toxicological studies using experimental animals (Hooser et al., 1988; McCollister et al., 1974). Chronic toxicological studies have not shown a carcinogenic potential for chlorpyrifos. We discuss below the studies and their limitations.

1. Mice:

Dow Chemical Co. conducted a study of CD-1 mice (56 of each sex per dose) that were fed chlorpyrifos (purity not specified) at 0, 0.05, 0.5, and 1.5 mg/kg for 105 weeks (Warner et al., 1980, as cited in Dow, 1997). Survival rates were not available.

Histopathological examination revealed that mid dose males had a significant increase in incidence of liver hyperplastic nodules (p value not available). Male mice fed the low and mid level dose, and female mice fed the low dose of chlorpyrifos had a significant increase in spindle cell hyperplasia in the adrenal glands. These changes were not dose-related. Details on incidence levels were not reported.

2. Rats:

Groups of Sherman rats (25 of each sex, per dose) were fed 0, 0.01, 0.03, 0.1 or 3 mg/kg chlorpyrifos (97.2% pure) in diet for two years. Tumors observed did not appear to be treatment-related. This study was long enough in duration to qualify as a cancer bioassay (McCollister et al., 1974), but had severe limitations. Mortality rates for controls and treated male rats were high, at 60% and 64%. Among females, 56% controls and 45% of the treated groups did not survive the full term of the study. Also, histopathological analysis was done on the controls and the groups fed the highest doses of chlorpyrifos only. Statistical analysis was not available on the incidence of tumors (McCollister et al., 1974).

Dow Chemical Co. conducted another two year study of Fischer 344 rats (50 of each sex per dose) fed 0, 0.05, 0.1, 1.0 or 10 mg/kg (Young and Grandjean, 1988, as in Dow, 1997). Details on survival rates and tumor incidences were not available. There were no reports of increases in tumor incidences.

In a study of Sprague-Dawley male rats fed 100 ppm Dursban® (chlorpyrifos) in normal or fat-enriched diet (20% corn oil) for one year there were no treatment-related differences in tumor incidences. This study cannot be regarded as a cancer bioassay since the animals were fed only one dose, for a relatively short period of time and histopathological evaluation of tissues was not performed (Buchet et al., 1977).

3. Dogs:

Beagle dogs (four of each sex per dose) were fed 0, 0.01, 0.03, 0.1, 1.0 or 3.0 mg/kg chlorpyrifos in diet for two years. There were no unscheduled deaths during the treatment period and food consumption was not affected in treated dogs. Histopathological examination was done on controls, tissues of dogs that had received the highest dose, and any gross lesions detected in other groups. The authors observed "no alterations that were judged to be chlorpyrifos treatment-related." The mean liver-to-body weight ratio was increased ($p < 0.05$) in males that were fed the 3.0 mg/kg dose for two years, but not in the females fed the same dose (McCollister et al., 1974).

4. Chickens:

Groups of ten White Leghorn cockerels were fed gelatin capsules containing 1 mg/kg Dursban® (chlorpyrifos) or 100 mg of the

sodium salt of its metabolite TCP three times a week for 30 weeks (Miyazaki and Hodgson, 1972). The livers of the chickens treated with TCP were significantly heavier after 30 weeks of treatment. Histopathological evaluation of livers was not performed. This study was too short to be a cancer bioassay.

5. Cats:

Adult male cats (six / group) were given an oral dose of either 40 mg/kg chlorpyrifos in olive oil and methylene chloride, the chlorpyrifos dose followed by 0.2 mg of atropine sulfate, or just the olive oil and methylene chloride (Hooser et al., 1988). No chlorpyrifos-related lesions were observed after 56 days of treatment. This study was a toxicological evaluation and should not be regarded as a cancer bioassay since it was a relatively short-term study using small numbers of animals.

6. Summary, Animal Studies:

Chronic toxicity studies in rats, dogs, cats and chickens treated with chlorpyrifos have not indicated an increased incidence of cancer in association with treatments with this insecticide. However, all these studies had many limitations that do not permit an evaluation of the carcinogenic potential of chlorpyrifos. The studies in rats were either limited by small numbers and low survival rates (McCollister et al., 1974), or by the inappropriate use of only one dose and short duration (Buchet et al., 1977). Sufficient details were not available for a critical evaluation of the unpublished studies in mice and rats. Dogs and chickens fed chlorpyrifos or the metabolite TCP were reported to have increased liver weights. However, a histopathological examination into the cause of the liver weight gain was not performed (McCollister et al., 1974; Miyazaki and Hodgson, 1972). One study in cats did not observe any treatment-related lesions, but was of short duration and had a very small number of animals.

C. Current Classification of Carcinogenicity by Other Agencies

1. IARC Classification:

The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenic potential of chlorpyrifos (ATSDR, 1997).

2. NTP Classification:

Chlorpyrifos has not been classified by the National Toxicology Program (NTP) (USDHHS, 1998).

3. EPA Classification:

Chlorpyrifos has been classified in Group D: not classifiable as to its carcinogenicity. This classification is based on inadequate evidence from studies of carcinogenicity in experimental animals (ATSDR, 1997).

V. Critical Evaluation on Breast Cancer Risk

A. Human Studies:

No studies were located on the incidence of breast cancer in women following exposure to chlorpyrifos.

B. Experimental Animal Studies

1. Rats:

There has been only one cancer bioassay of chlorpyrifos in rats. Groups of Sherman rats (25 of each sex, per dose) were fed 0, 0.01, 0.03, 0.1 or 3 mg/kg chlorpyrifos (97.2% pure) in diet for two years. Only 55% of the treated animals and 44% of controls survived the full two years. Histopathological examination was limited to any observed lesions, and of the groups fed 0 or 3.0 mg/kg chlorpyrifos. The tumors observed in treated animals and controls are listed in Table 1. Statistical analysis was not available (McCollister et al., 1974). There were no consistent or dose-related change in the incidence of mammary neoplasms in chlorpyrifos-treated rats.

Table 1. Mammary Gland Lesions Observed in Chlorpyrifos-Treated Female Sherman Rats

Type of Mammary Gland Lesion	Chlorpyrifos Treatment Dose (mg/kg)					
	0.0	0.01	0.03	0.10	1.0	3.0
fibroadenoma	2	2	2	1	3	3
cystadenomas	0	0	1	0	1	0
adenocarcinomas	0	0	0	1	0	0
adenomas	0	0	1	0	0	0
# that survived two years	11	14	14	13	17	10

2. Summary, Animal Studies on Breast Carcinogenicity:

Only one study in rats has reported the incidence of mammary tumors. This study did not observe a difference in mammary tumor incidences in chlorpyrifos-treated and control rats. The low number of surviving animals do not allow for a meaningful conclusion about chlorpyrifos' breast carcinogenicity (McCollister et al., 1974).

C. Other Relevant Data on Breast Cancer Risk

1. Evidence of Endocrine Disruption

a. In Vivo Studies:

Groups of ewes (six) were given capsules containing either gelatin or 12.5 mg/kg chlorpyrifos two times a week for 43 days. Serum concentration of thyroxine was significantly decreased in treated ewes, while serum concentration of cortisol was significantly increased ($p < .05$). The authors suggest that the effect on thyroxine could be due to competition for thyroid-binding-proteins, while the effect of increased cortisol can often be stress-induced. The basal luteinizing hormone levels or serum estradiol concentrations were not significantly different in treated animals compared to controls (Rawlings et al., 1998). The thyroid hormones can fluctuate in response to other environmental stresses, and these effects may or may not be chlorpyrifos treatment related. This study indicates that the serum estradiol levels are maintained in treated animals.

In another study, neonatal rats (8 per group, strain not specified) were treated with sub-cutaneous sublethal injections of 0, 14 mg/kg or 7 mg/kg technical grade chlorpyrifos (of unspecified purity) in corn oil for 15 days. The authors report that the treatments did not affect the survival or growth of the animals (Ahmad et al., 1993). The weight of the uterus and ovaries and serum concentration of estradiol was significantly decreased at the highest dose ($p < 0.01$) as well as the lower dose ($p < 0.05$) compared to controls. In the male rats, organ weights of the testes and epididymis, vas deferens, and prostate as well as the serum testosterone concentrations were significantly decreased at both doses ($p < 0.05$ at the lower dose and $p < 0.01$ at the higher dose). Since total body weights of the rats at the end of the treatments were not reported, it is difficult to assess if the ratio of organ weight / total body weight was affected, or whether these weight differences were indicative of a general reduced body weight. Chlorpyrifos seems to affect the reproductive development of both sexes. However, it cannot be determined if this effect was due to general toxicity or a suppression of gonadal steroid synthesis from this study.

b. In Vitro Assay for Estrogenicity:

The E-SCREEN assay uses the proliferative response of Michigan Cancer Foundation human breast cancer cells (MCF-7) to screen estrogen-mimics. Estrogen and estrogen-mimics can trigger an increase in mitotic activity in the estrogen-responsive cells.

Chlorpyrifos was not found to be estrogenic by this screening assay (Soto et al., 1995).

c. Effect on Spermatogenesis:

Dursban® 44 (43.2% chlorpyrifos, 56.8% inert ingredient mixed with petroleum distillate), was poured over the withers of 185 AI Holstein bulls for lice control. Seven of the bulls died, and six others got very sick indicating that the dose exceeded the maximum tolerated dose for bulls. The chlorpyrifos treatment caused a significant decrease ($p < 0.01$) in the total usable sperm that could be recovered from frozen ejaculates for six months (Everett, 1982). A decrease in spermatogenesis can be an indicator of decreased gonadal steroidogenesis and endocrine disruption. However the effect observed in this study was significant only in the recovery of sperm from frozen ejaculates and it was not clear whether chlorpyrifos treatments reduced spermatogenesis or the freeze-resistance of sperm.

2. Reproductive and Teratogenic Effects:

Reproductive toxicity may be suggestive of either endocrine disruption or embryo toxicity. We have included below any studies on reproductive toxicity of chlorpyrifos that indicate an effect on estrogen-dependent reproductive events. However, we have not included reports on chlorpyrifos' reproductive toxicity that indicate its developmental toxicity.

The state of Florida's Teratogen Information Services reported that it has received at least two inquiries about possible teratogenic effects of paternal exposure to chlorpyrifos (Poynor et al., 1997). Details on these inquiries were not reported.

First trimester *in utero* exposure to chlorpyrifos was implicated in four case reports of children (two girls and two boys) born with multiple birth defects. Two of the cases were siblings. The mother had been exposed in the first trimester of each of the two case pregnancies to a chlorpyrifos spray that had been used on the carpets to control fleas. The other two cases had one confounding exposure each, to chlordane and a product called firefog, which was used as a deodorant after a small electrical fire. All four cases had structural deformities of the brain and central nervous system, and three of the four cases had abnormal genitalia (Sherman, 1996; Sherman, 1995). Reports on ten adverse reproductive outcomes were submitted to the EPA by DowElanco, as cited by (Sherman, 1997). It is difficult to determine if chlorpyrifos caused the birth defects from these case reports. However, these reports indicate the need for precautions against exposure for pregnant women, and the need for larger case-control studies to evaluate whether chlorpyrifos exposures are associated with a higher risk of birth defects.

In an animal study, Sprague-Dawley rats (30 of each sex per dose) were given 0, 0.1, 1.0, or 5.0 mg/kg chlorpyrifos (96.6% pure) in

diet for 10 weeks. Rats from the F₁ litter were randomly divided into groups and treated to the same chlorpyrifos doses for 12 weeks, and mated to produce the F₂ litter. Males and females given 5 mg/kg chlorpyrifos had reduced weight gain which was consistent with the reduced feeding observed for females. Male and female pups from this high dose group had significantly reduced body weights ($p < 0.05$) (Breslin et al., 1996). The authors report that all other reproductive indices such as length of gestation, time to mating, litter size, litter sex ratio were not significantly affected by treatments. They did observe a significant decrease ($p < 0.05$) in the fertility and conception index of females that were fed 0.1 mg/kg chlorpyrifos, but the decrease was not significant in the groups fed the higher doses, indicating a lack of dose-related response.

In another study, groups of CF-1 mice were treated by gavage to 0, 1, 10 or 25 mg/kg chlorpyrifos in cottonseed oil on days 6 through 15 of gestation. The 25 mg/kg dose caused maternal toxicity and significant decrease in fetal body weight ($p < 0.05$). Chlorpyrifos treatments at other levels did not affect the body weight gain in the other groups of treated dams (Deacon et al., 1980).

Reproductive studies indicate that chlorpyrifos can be toxic to the fetus when absorbed through the placenta and can affect the weight gain of the litter. Chlorpyrifos does not reduce the fertility or the conception rate of the treated females in animal studies.

3. Tests of Mutagenicity and Genotoxicity:

Mutagenicity studies of chlorpyrifos in animals, insects and cell culture have given equivocal results. Chlorpyrifos has been consistently non-mutagenic in bacteria and yeast.

a. Studies in Animals:

Swiss mice were tested for induction of micronuclei in the bone marrow following intraperitoneal (i.p.), oral and dermal exposure to chlorpyrifos. Repeated oral or i.p. exposures to chlorpyrifos caused a significant induction ($p < 0.01$) in the percentage of polychromatic erythrocytes with micronuclei in the bone marrow (Amer and Fahmy, 1982). Dermal exposures did not induce micronuclei in this study and the effect on micronuclei following oral exposures was reversible after a recovery period of seven days. Another study used oral gavage treatments of CD-1 mice with chlorpyrifos did not report an induction of micronuclei in the bone marrow (Gollapudi et al., 1995). Chlorpyrifos and its metabolites did not induce sister chromatid exchange (SCE) frequency in a three-day chick embryo (Muscarella et al., 1984). One study observed liver DNA-associated radioactivity after i.p. injection of mice with radioactively labeled chlorpyrifos. However, the DNA fractions were not analyzed to determine if chlorpyrifos had truly induced DNA-alkylation (Mostafa et al., 1983).

b. Studies in Insects:

A commercial preparation of chlorpyrifos (50 ppb, purity unspecified) caused a significant induction in the rate of loss of the ring-X chromosomes (complete chromosome loss), but not the Y chromosomes marker (partial chromosome loss) in a *Drosophila* screening assay for genetic damage (Woodruff et al., 1983). A farm-grade formulation of chlorpyrifos was found to cause a significant increase ($p < 0.05$) in the frequency of sex-linked recessive lethals (SLRL), and in the frequency of mosaic spots indicative of somatic mutations (Patnaik and Tripathy, 1992). In contrast, chlorpyrifos (0.1 ppm) itself did not induce SLRL in *Drosophila* in another study (Sandhu et al., 1985).

c. Studies in Bacteria and Yeast:

Chlorpyrifos has not been found to be mutagenic in most screening assays in bacteria (Gentile et al., 1982; Kada et al., 1980; Sandhu et al., 1985; Shirasu et al., 1976). Short-term assays done by the Japanese Ministry of Health and Welfare found chlorpyrifos to be non-mutagenic in *Salmonella* and *Bacillus* (rec assay) with or without metabolic activation (Kawachi et al., 1980a). A study reported as an abstract found chlorpyrifos to be non-mutagenic in bacteria (*Salmonella typhimurium*) and yeast (*Saccharomyces cerevisiae*) (Waters et al., 1982). Chlorpyrifos was not found to be mutagenic in an assay in *Salmonella* (Hour et al., 1998) and by the Ames test (Gollapudi et al., 1995).

d. Studies in Isolated Human and Animal Cells:

Treatments of male Fischer 344 rats with chlorpyrifos (7.6 mg/kg gavage) caused an increase in expression of the multidrug resistance (mdr) gene product P-glycoprotein (P-gp) along the digestive tract (Lanning et al., 1995). This study raised a concern about the potential of exposure to chlorpyrifos causing multidrug resistance in cancer cells of patients receiving chemotherapy. Exposure of MCF-7 breast cancer cells *in vitro* with chlorpyrifos however, did not cause an induction in the expression P-gp (Lanning and Fine, 1995). One concern that remains is whether the activated metabolite, chlorpyrifos-oxon, may cause an increased expression of P-gp. Chlorpyrifos-oxon was found to stimulate P-gp ATPase activity in an insect cell assay system (Lanning et al., 1996). However, other studies have shown that chlorpyrifos-oxon is rapidly hydrolyzed and may not be found outside the liver of mammals (see Section V.C.5). Further animal studies are needed to determine if exposure to pesticides reduces the responsiveness of tumors to chemotherapy.

Dursban® (chlorpyrifos) at 2 and 20 µg/ml, was found to significantly induce ($p < 0.01$) SCE in human lymphoid cells *in vitro* (Sobti et al., 1982). Metabolic activation with S9 preparations (liver microsomal extract) did not cause a significant potentiation of the genotoxic effect observed in this assay. In contrast, in another study chlorpyrifos (99% pure) did not significantly induce SCE in cultured human lymphocytes (Nelson et al., 1990). Further,

treatments of Chinese hamster ovary (CHO) cells with 1, 10 or 100 µg/ml of chlorpyrifos did not induce SCE frequency (Muscarella et al., 1984). There was also no evidence of chromosome aberrations in blastocysts from superovulated cows crossed to Dursban® 44 (chlorpyrifos) treated bulls in the same study. Microsome-activated chlorpyrifos was found to induce chromosome aberrations in CHO cells, but was not mutagenic in a series of other genotoxicity assays (Kawachi et al., 1980b). Chlorpyrifos did not cause mutations or chromosome aberrations in CHO cells and rat lymphocytes in another study (Gollapudi et al., 1995). Hence, results of studies of chlorpyrifos genotoxicity in different cell systems are equivocal.

4. Evidence of Tumor Promotion:

In a study that has been reported only as an abstract, concurrent treatments of male F344 rats with chlorpyrifos and the herbicide atrazine after a leukemia transplant, caused leukemia to develop earlier than in rats that received the transplant alone (Dieter and Garnett, 1993). This study indicates that the combination of chlorpyrifos and atrazine may promote leukemia in rats. Details on the study were not available. It is not clear if the difference was significant and if it occurred for either chemical separately.

F344 rats that had been injected with a single dose (200 mg/kg) of the carcinogen diethylnitrosamine (DEN) were fed a combination of 20 different pesticides including chlorpyrifos, at either their acceptable daily intake (ADI) level, or at 100 times the ADI. Glutathione S-transferase P (GST-P) foci were assayed as pre-neoplastic indicators of a carcinogenic effect. The mixture of pesticides including chlorpyrifos was found to significantly increase ($p < 0.05$) the incidence of GST-P positive foci in the liver of DEN-treated rats at 100 times the ADI, but not at the ADI levels (Ito et al., 1995). Since chlorpyrifos was just one of the chemicals in the tumor promoting mixture, its role as a liver tumor promoter cannot be determined from this study.

5. Effects on Hepatic Enzymes:

Studies in experimental dogs and chickens discussed in IV. B. have reported liver enlargement in response to chronic treatments with chlorpyrifos (McCollister et al., 1974; Miyazaki and Hodgson, 1972). A detailed histopathological analysis or enzyme profile assay was not done to determine if the liver enlargement was caused by the stimulation of specific liver enzymes. In one study of C57BL6 mice (100) that were housed in 27 by 48 cm shoeboxes with 12 grams of Dursban® (chlorpyrifos) granules in bedding for nine days, there was no significant treatment-related effect on the liver microsomal enzymes (Pence et al., 1991).

In an *in vitro* study, chlorpyrifos was shown to induce hepatic lipid peroxidation, assayed as a dose-dependent increase in the production of malondialdehyde (MDA) (Yamano and Morita, 1993). Theoretically, peroxidative effects have the potential to

cause DNA damage in the liver. However, DNA damage has not been studied in the liver of rats treated with chlorpyrifos.

6. Immunological Effects:

Case reports below have implicated chlorpyrifos exposure as causing immunotoxic effects, but the evidence from case-reports alone is inadequate to evaluate a cause and effect relationship. Further, details on possible immunotoxic effects of the kind that affect cancer risk were not available. However, these case reports suggest that chlorpyrifos-exposed individuals should be studied for immunotoxic effects. We recommend that future studies include an evaluation of immunological parameters that could affect cancer risk.

Twelve patients (four men and eight women) with unexplained health complaints and reported exposure to chlorpyrifos, were referred for immunological testing by their physician. One patient had been exposed during a toxic spill, but most of the patients were housewives exposed at home ($n = 8$) (Thrasher et al., 1993). There was a significant increase in the CD26 count (indicator of T cell activation) of exposed individuals ($p < 0.01$). The percentage of autoantibodies in the serum of exposed individuals was increased and $> 50\%$ of the individuals had two or more different autoantibodies. In another study, patients with multiple chemical sensitivity (MCS) were evaluated for any associations with chemical exposure. Of the 68 patients evaluated in this study, 12 had been exposed to chlorpyrifos, of which six had also been exposed to chlordane (Ziem and McTamney, 1997). A self-reported case study of a patient with MCS has implicated exposure to Dursban® (chlorpyrifos) (Berkson, 1994).

7. Summary, Other Relevant Data on Breast Cancer Risk:

Chlorpyrifos has not been found to be estrogenic in the E-SCREEN assay (Soto et al., 1995). Its possible endocrine disruptive effect in ewes (Rawlings et al., 1998) and other reproductive toxicity reports do not indicate an estrogenic effect (Breslin et al., 1996; Everett, 1982). Chlorpyrifos is not mutagenic in bacteria or yeast (Gentile et al., 1982; Hour et al., 1998; Kada et al., 1980; Kawachi et al., 1980b; Sandhu et al., 1985; Shirasu et al., 1976). The evidence on its ability to induce SCE in animals was equivocal (Amer and Fahmy, 1982; Gollapudi et al., 1995; Muscarella et al., 1984), as were results of genotoxicity studies in insects (Patnaik and Tripathy, 1992; Sandhu et al., 1985; Woodruff et al., 1983). One study reported as an abstract, found chlorpyrifos, in combination with atrazine, to promote the development of leukemia in rats (Dieter and Garnett, 1993).

VI. Other Information, Environmental Fate and Potential for Human Exposure

Chlorpyrifos is a widely used insecticide, with applications in agricultural as well as urban home use. It is one of the most popular indoor use insecticides. We have included below some of the studies that demonstrate the different routes of occupational, non-occupational, and children's' exposure to chlorpyrifos.

A. Occupational Exposure:

Orchard workers who handle plants treated with chlorpyrifos were found to be exposed mainly through their hands and uncovered skin, but had the potential for respiratory exposure from reentry into treated areas (Aprea et al., 1994). Non-applicators who enter cornfields treated with chlorpyrifos (within 4 to 48 hours) were found to have the potential for both, dermal and respiratory exposure (Brady et al., 1991). In another study, dermal and respiratory exposure was evaluated for eight urban pesticide applicators during structural treatments with Dursban® (Fenske and Elkner, 1990a). Chlorpyrifos metabolite TCP was found present in all urine samples collected 24 to 48 hours after the workshift. An average estimated daily dose for workers was estimated to range between 0.01 to 0.015 mg/kg/day, with dermal routes contributing two-thirds of the dose. Chlorpyrifos levels in the air of moving vehicles used by pest control operators were found to be significantly higher ($p < 0.01$) than the air in stationary vehicles (Wright et al., 1982). These studies indicate that the main route of exposure among workers is dermal, with varying levels of respiratory exposure.

The frequency of exposure among workers has been observed to be high. An occupational study on 22 pest control operators from a company in Houston, Texas, found dialkyl phosphate metabolites in 96% of the urine samples taken within eight hours of OP applications (Hayes et al., 1980). Urine samples from employees who were not involved in application had very low levels of metabolites. Urine samples from male pest control operators who sprayed chlorpyrifos over seven days of monitoring indicated high levels of the metabolite dialkyl phosphate (Takamiya, 1994).

Further, some reports indicate that masks, gloves and coveralls do not prevent all exposure, especially when applicators are spraying this insecticide. Termite control workers (eight males, 26 to 49 years of age) were monitored for plasma cholinesterase inhibition and urinary levels of the TCP metabolite. The workers wore hoods, overalls, rubber gloves and boots, and a mask for protection, but were still reported to have respiratory and dermal exposure (peak TCP in urine = 4 mg/g creatinine) (Jitsumari et al., 1989). Occupational exposure among workers who sprayed areas for control of mosquitoes had depressed plasma cholinesterase levels post-exposure, despite the use of masks and gloves (Eliason et al., 1969). Applicators who treat crawl spaces

against termites were potentially exposed to 5.6 to 26.6% of the TLV for chlorpyrifos during applications following label directions and using a proper respirator (Leidy et al., 1991). Dermal and respiratory exposures to applicators using a spray of Killmaster II® (2% chlorpyrifos) were found to be higher than for paint-on applications (Gold et al., 1981).

These studies indicate the need to evaluate the effectiveness of the protective clothing worn by applicators, especially sprayers. Synthetic disposable coveralls were found to offer more protection to greenhouse applicators, with a penetration rate of 3%, compared to reusable treated twill coveralls (19% penetration) (Nigg et al., 1993). Another study reports that a 3-hour soak in 0.4% solution of liquid chlorine bleach reduces chlorpyrifos residues on overalls to less than 1% (Laughlin, 1993).

B. Potential of Exposure for the General Population:

A program at Oregon State University provides consultation services to the public regarding pesticide-related illnesses. A report from this program indicates that chlorpyrifos was the subject of 37 of the 300 total inquiries that were handled in the first 20 months of the program (Wagner, 1990). With increasing use of this insecticide, the potential for exposure of the general population is also increasing.

1. Food and Water:

Food placed in a room 0.5 hours and 4.5 hours after crack and crevice treatment with 0.5 to 1% solution of chlorpyrifos had non-detectable, or < 0.02 ppm of chlorpyrifos (Jackson and Wright, 1975). Based on one Food and Drug Administration (FDA) study, it is estimated that the average daily intake of chlorpyrifos through food and water was 0.001 to 0.005 $\mu\text{g/kg}$ (Cantilli, 1991). FDA also conducts studies to determine the level of different pesticide residues that remain in a typical meal or menu items, called "Total Diet Studies." A FDA Total Diet Study estimated dietary exposure to chlorpyrifos to be 0.8 to 0.9 $\mu\text{g/day}$ (MacIntosh et al., 1996). A dietary risk assessment study conducted by the Department of Pesticide Regulation, California concluded that the tolerances for chlorpyrifos provided an adequate margin of safety against potential acute dietary exposure (Cochran et al., 1995).

The half-life of chlorpyrifos in water has been estimated to be < 24 hours (Racke, 1993). Chlorpyrifos has been detected in some rivers, but the flux represented a very low percentage of the amount applied in the surrounding agricultural areas (Larson et al., 1995). It was found at detectable levels in some shallow groundwater samples from areas around corn and soybean cultivations, and orchard and vineyards, at concentrations that were much lower than the HA in drinking water. It was not detected in 21 wells and two springs located in a mostly agricultural watershed in Pennsylvania (Pionke and Glotfelty, 1989). Chlorpyrifos detection in the watershed from agricultural regions into the Canadian Great

Lakes were rare in 1975-1977 (<1%) (Frank et al., 1982), and chlorpyrifos remained a minor pesticide contaminant in the agricultural drainage into the Lake Erie Basin between 1983 to 1991 (Richards and Baker, 1993). Chlorpyrifos has been found to be more stable in polluted waters, especially at lower temperatures (sub-ambient) (Schaeffer and Dupras, 1970). An accidental spill of chlorpyrifos (unknown amount) into a tropical marine bay caused extensive fish kill, but the water levels of the contaminant were reduced to < 0.3 µg/L in 23 days (Cowgill et al., 1991). Fish levels of chlorpyrifos decreased exponentially from 96 µg/kg in the first few days to 0.4 µg/kg after 23 days.

2. Air:

A “Non-Occupational Pesticide Exposure Study” was designed to assess season variations and total combined exposure through air, diet, dermal contact and water in 216 homes in two different geographic regions, Jacksonville, Florida and Springfield/Chicopee, Massachusetts (Whitmore et al., 1994). Indoor and outdoor air contamination with chlorpyrifos was very frequent (88 to 100% of samples). The mean air concentrations ranged between 120.3 to 366.6 ng/m³ indoors, and 16.7 ng/m³ outdoors in summer in Jacksonville. Only the outdoor air had decreased frequency of contamination in Spring and Winter. In Springfield/Chicopee, indoor air contamination was relatively less frequent (30%; mean air concentration 5.1 to 9.8 ng/m³). Outdoor air contamination was observed only in Spring (52%; mean air concentration 13.9 ng/m³). Air exposures were higher than the dietary exposure estimated from market basket surveys in Jacksonville, but the level of dietary and air exposure were very similar in Springfield/Chicopee.

Another four-season study in Louisiana analyzed the air quality of 53 homes (rural and urban) for chlorpyrifos (Lemus et al., 1997). The selection procedure for the homes was not defined. As in the previous study, summer and spring levels were higher. The state of Florida has a more stringent regulation on the maximum concentration of air residues of chlorpyrifos that are acceptable for an eight hour exposure period (2 µg/m³). In summer, the air in 25% of the urban houses and 14% of the kitchen area samples exceeded this level. In 26% of the homes, the insecticide was stored in aerosol cans under the kitchen sink. Pest strips containing chlorpyrifos were shown to emit a peak concentration of 0.23 µg/m³ insecticide seven days after installation in a room, following manufacturer’s guidelines (Jackson and Lewis, 1981). In another study, homes treated with a chlorpyrifos spray by the homeowner or a professional service had indoor residue levels of 140 ng/m³ and 150 ng/m³, respectively (Anderson and Hites, 1988).

Chlorpyrifos has been shown to penetrate the air of homes in which the crawl space or concrete slabs have been treated against termites (Wright et al., 1988). Chlorpyrifos levels were detectable

in the kitchens and bedrooms four years after application, with mean concentrations ranging from 2 to 6 µg/m³ (Wright et al., 1991). The levels fell to < 0.1 to 0.7 µg/m³ after eight years (Wright et al., 1994). A film of plastic was shown to be an effective barrier in preventing chlorpyrifos from crawl spaces from penetrating the air of homes (Moye and Malagodi, 1987).

Airborne and surface concentrations of chlorpyrifos were measured in seven offices that were treated with Dursban® sprays. The airborne concentrations peaked at 27 µg/m³, after four hours, but in many cases, the surface concentrations were higher at 24 or 48 hours after spraying (5.9 ng/cm²). Although the airborne levels in this study were within the TLV assigned for chlorpyrifos, it indicates that occupants should be warned to remove coffee cups and other personal articles prior to pesticide treatments (Currie et al., 1990).

Chlorpyrifos was detected at levels ranging from 170 to 6,500 ng/L in fog water samples collected from different regions in San Joaquin Valley, California, indicating the enrichment factor in fog droplets to be as high as 260 in some regions (Glotfelty et al., 1987). Small, but detectable levels of chlorpyrifos were found in the air and water samples collected from high altitudes of the Sierra Nevada mountains. Peak concentrations of these residues corresponded with seasons of extensive spraying in farms and orchards of the California Central Valley (Zabik and Seiber, 1993).

3. Residential Surfaces:

A study has analyzed surfaces and toys accessible to children to estimate the amount of exposure to children after residential use of chlorpyrifos (Gurunathan et al., 1998). Two apartments in New Jersey were sprayed with 0.5% chlorpyrifos solution following label directions. Air, surface and toys were sampled, four to 336 hours after application. The study found that plush felt toys and furniture could serve as a sink and collect chlorpyrifos residues. Non-dietary exposure potential to a three to six year old child from hand to mouth, and dermal routes was estimated at of 208 µg/kg/day for one week following treatment (Gurunathan et al., 1998). These high levels of exposures were theoretical estimates based on absorption rates observed in other studies, and were not levels that were monitored. This study has raised a lot of concern and comment about the risk of chlorpyrifos exposure to children following its residential use (Davis and Ahmed, 1998; Gibson et al., 1998). While exposures as high as 21 to 119 times the reference dose (RfD) have been demonstrated as possible (Davis and Ahmed, 1998), these are still theoretical estimates since actual exposures were not monitored in the study (Gibson et al., 1998). Two other studies summarized below, have also demonstrated exposures to toddlers following home use of chlorpyrifos by analyzing the residues in hand rinses.

House dust samples (114) were collected from middle-income households (nine) with a child of six months to five years of age in Durham, North Carolina and analyzed for pesticide residues (Lewis et al., 1994). Chlorpyrifos was found in the carpet dust in five out of the nine houses. The mean concentration of chlorpyrifos in different samples was $1.3 \mu\text{g}/\text{m}^2$, with the highest concentrations being found in entryway soils of homes that had been recently treated (within two days) with the insecticide. Two of four children had chlorpyrifos residues in hand rinses ($0.06 \mu\text{g}$) that corresponded to the carpet dust load in the house. Exposure to children was estimated to range between 0.07 to $7.5 \mu\text{g}/\text{day}$ from air and 0.04 to $0.29 \mu\text{g}/\text{day}$ from house dust. In another study, chlorpyrifos was detected in the house dust of all seven houses in New Jersey that were sampled, at levels ranging from 530 ng/g to $15,000 \text{ ng/g}$ (Roinestad et al., 1993). The dust levels were found to be higher eight weeks after application (700 ng/g), than immediately after application (655 ng/g) in the one home that was sampled twice. A similar survey of homes in California found 0.2 to 33 ppm chlorpyrifos in house dust from eleven homes. Chlorpyrifos residues were also detected on the hands of three of the eleven toddlers (Bradman et al., 1997).

Air residues of chlorpyrifos in homes treated with the insecticide indicate a higher concentration in the air at the infant breathing zone, or 25 cm above the carpet, with time-weighted averages of 41.2 and $66.8 \mu\text{g}/\text{m}^3$ in ventilated and non-ventilated rooms, respectively. These values exceed the interim guidelines set by the National Academy of Sciences of $10 \mu\text{g}/\text{m}^2$ of chlorpyrifos for indoor air following termiticide treatments (Fenske et al., 1990b). Dermal exposures were estimated to be 250 and 527% of the No Observable Effect Level (NOEL) on the first day, and 127% and 183% of NOEL on the second day, for ventilated and non-ventilated rooms respectively. In another study of indoor application, low levels of chlorpyrifos (0 to $0.06 \mu\text{g}/\text{cm}^2$) were still detectable in swipe samples 42 days after the treatment of dormitory rooms (Wright et al., 1984).

The above studies indicate non-dietary ingestion and dermal contact with surfaces as an important route of exposure, especially for children. Additional safeguards such as well-defined re-entry periods, and advice for keeping toys away from treated rooms for at least a week during and following applications should be strongly advised in homes with small children. This is especially a concern for chlorpyrifos since it is widely used in residential settings. In addition, toxicological studies indicate that the percutaneous absorption rates and / or the susceptibility of newborn pigs (Long et al., 1986) and calves (Palmer et al., 1980) is higher than the corresponding adult animals. It is not known if infants and children are more susceptible to chlorpyrifos exposure than adults in humans. These results call for extra caution while considering the levels of exposure for children. The principal

manufacturer and registrant of chlorpyrifos and the EPA have reached an agreement to take steps to reduce the risk of high exposure to children by limiting its residential uses (see Section III A.)

4. Soil:

The low solubility in water combined with high adsorption to soil surfaces contributes to the relative immobility and low bioavailability of chlorpyrifos. Chlorpyrifos is non-systemic and is not taken up by the plants from contaminated soils. The surface runoff rates of chlorpyrifos are low, except as adsorbed to soil particles (Larson et al., 1995). Hydrolytic degradation represents the major route of dissipation, with increasing temperature favorably modulating the dissipation rates. The half-life of chlorpyrifos in soils estimates range from one to 16 days (Racke, 1993) to 30 days (Larson et al., 1995). The degradation half-life for chlorpyrifos in orchard soils was estimated at 10 days (Redondo, 1997).

The half-life of chlorpyrifos in the field can vary greatly depending on the application rate, soil type, and environmental variables such as temperature and moisture (Racke, 1993). One study found homes treated against subterranean termites to have 0 to 1684 ppm of chlorpyrifos in the exterior soil four years later, and 0 to 439 ppm eight years after treatment (Wright et al., 1991; Wright et al., 1994). The authors suggest that the environment around the inner walls of the foundations of homes and the soil type may have contributed to the chlorpyrifos stability observed in this study.

C. Storage and Excretion of Chlorpyrifos in Mammals:

The pharmacokinetics of chlorpyrifos (99.8% pure) was investigated in six healthy white male volunteers after oral (0.5 mg/kg) and dermal (5 mg/kg) exposure (Nolan et al., 1984). Plasma cholinesterase was depressed after the oral and dermal exposures. Blood concentrations after either route of exposure were very low ($< 30 \text{ ng/ml}$). Urine is the major route of excretion in humans and mice through either dermal or oral exposure (Nolan et al., 1984; Shah et al., 1981). Urine samples from exposed humans had peak concentrations of TCP metabolite on the day following oral exposure. The excretion of TCP had a broader peak for dermal exposure. No unmodified chlorpyrifos was detected in the urine. The half-life of chlorpyrifos in the human body was estimated to be 27 hours (Nolan et al., 1984).

Another study estimated the half-life in humans to be 3.5 to 5.5 hours based on three cases of chlorpyrifos poisonings (Vasilic et al., 1992). However, the effect on serum cholinesterase enzymes was found to persist for many days after the poisonings in this study.

1. Lactation and Breast Milk:

Lactating cows fed 0.04 to 0.17 mg/kg chlorpyrifos in silage had no detectable levels of chlorpyrifos or its oxygen analog in milk (Johnson et al., 1969). A Russian study (as reported in the abstract) found a single spraying of 0.15% Dursban® (chlorpyrifos) on cows to cause detectable levels of chlorpyrifos in milk for four days and the highest amount detected was 0.304 mg/ml (Leshchev et al., 1972). Chlorpyrifos was not detected in milk and dairy products surveyed by the FDA between 1978 to 1979 (Gartrell et al., 1985).

2. Adipose Tissues:

Female sheep (n = 22) dermally treated with chlorpyrifos formulation had low levels of chlorpyrifos in omental (stomach fold) fat (0.008 to 0.427 ppm) one week post-treatment, but the levels fell to non-detectable within four weeks (Ivey and Palmer, 1981). In cattle that were repeatedly dipped in 0.025% emulsions of chlorpyrifos, the highest residues in fat (2 ppm) were found one week after the second and third dippings (Ivey et al., 1972). This study found as much as 76% of the residues in fat to be retained after cooking.

Studies in rats indicate that 90% of a single dose of radioactively labeled chlorpyrifos can be recovered from the urine within a day (Bakke et al., 1976; Smith et al., 1966). The major metabolites were identified as 3,5,6-trichloro-2-pyridinal phosphate (75 to 80%), TCP (15 to 29%), and traces of O,O-diethyl-O-3,5,6-trichloro-2-pyridyl phosphorothioate. Only the trace amounts of phosphorothioate were expected to accumulate in the fat tissues, but the amount of radioactivity in fat tissues was too low to allow identification (Smith et al., 1966).

3. Tissue Distribution:

The liver is the main site of chlorpyrifos metabolism. Studies in whole animals and perfused liver indicate a rapid clearance of chlorpyrifos from the liver (Cantilli, 1991; Sultatos et al., 1985; Sultatos and Murphy, 1983). Tissue levels of chlorpyrifos were <1 ppm in rats that were orally exposed to the insecticide (Cantilli, 1991). Chlorpyrifos can be activated to its oxygen analog (chlorpyrifos-oxon) in the liver of mammals. This activated oxon, when treated with mouse hepatic microsomes *in vitro* was rapidly hydrolyzed by the microsomal esterases (Sultatos and Murphy, 1983). *In situ* perfusion of mouse liver with chlorpyrifos-oxon also indicated rapid detoxication and no chlorpyrifos-oxon was detected to be released from the liver of mice (Sultatos et al., 1985). However, rat liver perfusion with chlorpyrifos showed a net activation of the insecticide to its oxon in the rat. Livers from male rats eliminated significantly more chlorpyrifos-oxon than the livers of female rats ($p < 0.05$). Although the female livers were found to be better at hydrolyzing activated chlorpyrifos, the female rats have been found to be more susceptible to the toxicity of this insecticide than males in whole animal studies (Sultatos, 1991).

VII. Summary and Recommendations for Breast Cancer Risk Classification

Breast Cancer Risk:

We propose that chlorpyrifos be classified in Group 3, *not classifiable as to its breast carcinogenicity in humans* (please see Appendix B for an explanation of the BCERF Breast Cancer Risk Classification Scheme). This is based on the following:

Human studies: There are no studies available to assess the breast carcinogenic potential of chlorpyrifos in humans.

Animal studies: One study in experimental rats treated with chlorpyrifos has not observed an increased incidence of mammary tumors in treated animals, but this study evaluated a very small number of animals that survived the treatment period (McCollister et al., 1974).

Related mechanisms: Chlorpyrifos has not been found to be estrogenic (Breslin et al., 1996; Soto et al., 1995). It is not mutagenic in bacteria or yeast (Gentile et al., 1982; Hour et al., 1998; Kada et al., 1980; Kawachi et al., 1980b; Sandhu et al., 1985; Shirasu et al., 1976). Results on its genotoxic effects in other systems were equivocal. Chlorpyrifos was found to induce SCE in human lymphoid cells *in vitro* (Sobti et al., 1982). We recommend that populations exposed to high levels of chlorpyrifos be followed for genotoxic and immunotoxic effects.

While the evidence above does not show that chlorpyrifos increases breast cancer risk, it should be noted that gaps in research do not allow a conclusion. Chlorpyrifos is known to have toxic effects on the nervous system of humans and animals and should be used with caution (USEPA, 1996). Chlorpyrifos is widely used in urban and agricultural areas. Exposure to this insecticide has been frequent and well documented among sprayers and applicators. Its increasing use in homes, offices, schools and other facilities creates the potential for exposure of the general population, including children.

VIII. Identification of Research Gaps, and Other Recommendations:

- Urine analysis of applicators has documented a high potential of exposure to this insecticide. Further studies are needed on protective apparel and ways to reduce the potential of exposure to this insecticide among applicators and manufacturing workers.
- Chlorpyrifos has been widely used as an insecticide for more than two decades. Except for one study in which there was only one case exposed to this insecticide (Zahm and Babitt, 1993), there have been no studies of cancer incidences in populations that may have been exposed through their

occupation. Large-scale epidemiological studies of applicators and manufacturing workers who were exposed in the past are needed to determine if chlorpyrifos has the potential to affect cancer risk.

- The above populations should also be monitored for immunotoxic effects.
- The animal studies done so far had several limitations. We recommend that companion and farm animals that have been treated with chlorpyrifos or have worn flea collars be followed for cancer incidences.

IX. Summary of New Human Studies Currently Being Conducted:

Studies of Occupational Cancer—Pesticides

Alavanja, M., Blair, A., Zahm, S., NCI (extracted from the CancerNet at NCI and Personal Communication)

The “Agricultural Health Study” proposes to look at the relationship between exposures to agricultural chemicals, including pesticides, and cancer risk. Enrollment in this study includes 90,000 men and women farmers, pesticide applicators and farmer’s wives from Iowa and North Carolina. Besides conducting interviews to determine pesticide use, it will also seek information on lifestyle factors, medical and family history of disease and diet.

Perinatal / Juvenile Exposure to Pesticides on Adult Neural, Immune Function

Chapin, R.E. National Institute of Environmental Health and Safety (extracted from the CRISP Database).

An ongoing study will evaluate any reproductive, neurological or immunological effects from exposure of experimental animals to chlorpyrifos during developmental, perinatal and juvenile stages.

Occupational Injury in Hispanic Farmworker Families

McCurdy, S.A., University of California, Davis (extracted from the CRISP Database).

Migrant and seasonal workers in California will be evaluated for occupational injury in association with OP exposure, piece-work versus hourly pay, language appropriate safety training, and the role of multiple employment. The cohort is expected to consist of 500 farmworker families who live in six Migrant Housing Centers close to Davis, California.

Exposure to Chlorpyrifos and Other OP among mixer / loader / applicators applying dormant oil / OP Sprays to Almond Orchards

R. I. Krieger, University of California, Riverside (extracted from a meeting abstract)

Urine analysis will be used to survey the exposure of OP mixers, loaders and applicators to chlorpyrifos and other OP, to measure the extent of absorption and the protection offered by different clothings. Worker exposure will be surveyed in different indoor and outdoor settings in which chlorpyrifos is typically used.

Role of Chlorpyrifos in Gulf War Illnesses

A Presidential Committee on Gulf War Veteran’s Illnesses (extracted from the web site <http://www.gwvi.gov/ch4.html>)

Chlorpyrifos is one of the OP documented as being shipped for use during the Gulf War. A Presidential Committee on Gulf War Veteran’s Illnesses has reported on several risk factors in veterans of this war, including exposure to OPs including chlorpyrifos. This committee was terminated in November, 1997. However, the Center for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and the Agency for Toxic Substances and Disease Registry (ATSDR) have co-sponsored a conference with the aim of developing a research plan to investigate any relationship between chemical exposures and illnesses among Gulf War veterans (Dr. T.D. Spittler, Personal Communication).

X. Bibliography

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XI. Appendix A. Common Abbreviations, Acronyms and Symbols

ACGIH	American Conference of Governmental Industrial Hygienists	MCS	multiple chemical sensitivity
ADI	acceptable daily intake	MDA	malondialdehyde
AI	active ingredient	mdr	multidrug resistance
ATSDR	Agency for Toxic Substances and Disease Registry	mg	microgram
BCERF	Program on Breast Cancer and Environmental Risk Factors in New York State, based in Cornell's Center for the Environment, Institute for Comparative and Environmental Toxicology	mg	milligram
CAS	Chemical Abstract Service	MTD	maximum tolerated dose
CDC	Carworth Farm E strain rats	n	number of subjects/animals in the group
CfE	Cornell University's Center for the Environment	NCI	National Cancer Institute
CHO	Chinese hamster ovary	NHL	non-Hodgkin's lymphoma
CI	confidence interval	NIH	National Institutes of Health
Cl	chlorine	NOAEL	no observable adverse effect level
cm	centimeter	NTIS	National Technical Information Service; repository for federal agency technical reports
Co	company	NTP	National Toxicology Program
CRISP	Computer Retrieval of Information on Scientific Projects; database of scientific intra and extramural projects supported by the Dept. of Health and Human Services (i.e., NIH, EPA, USDA)	NY	New York
DEN	diethylnitrosamine	NYS	New York State
DNA	deoxyribonucleic acid	OP	organophosphate pesticide
EPA	Environmental Protection Agency	OR	Odds Ratio
E-SCREEN	screening assay for estrogenicity that measures proliferative response in estrogen-dependent breast tumor cells	P-gp	P-glycoprotein
FDA	Food and Drug Administration	ppb	parts per billion
GST-P	glutathione S-transferase P	ppm	parts per million
HA	The health advisories are non-enforceable limits of the concentration of the chemical in the drinking water that is not expected to cause any adverse noncarcinogenic health effects when consumed for no more than the time period specified, with a margin of safety	RfD	reference dose
IARC	International Agency for Research on Cancer, headquartered in Lyon, France	SCE	sister chromatid exchange
ICET	Institute for Comparative and Environmental Toxicology	SLRL	sex-linked recessive lethals
i.p.	kilogram	SMR	standardized mortality ratio, the ratio of deaths among a cohort, to the expected number of deaths, multiplied by 100
L	liter	TCP	3,5,6-trichloro-2-pyridinol
lbs	pounds	TLV	threshold limit value
m	Michigan Cancer Foundation; cells derived from human breast tumor	TWA	time-weighted average
MCL	Maximum Contaminant Level; enforceable limit set by EPA which sets the maximum level of a contaminate in a public drinking water supply	US	United States
		USDA	United States Department of Agriculture
		USEPA	United States Environmental Protection Agency
		WHO	World Health Organization

Symbols:

α	alpha
β	beta
γ	gamma
μg	microgram
μM	micromolar
ng	nanogram
<	less than
>	greater than
%	percent
p	p value
\pm	plus or minus
=	equal to
®	registered trademark

XII Appendix B. Critical Evaluations of Breast Cancer Risk

This includes an overview of the Critical Evaluations and explanation of the BCERF Breast Cancer Risk Classification Scheme

The Process

Starting Point - Existing Critical Evaluations on Evidence of Carcinogenicity

IARC Monographs (**I**nternational **A**gency for **R**esearch on **C**ancer)

NTP ARC (**N**ational **T**oxicology **P**rogram, **A**nnual **R**eport on **C**arcinogens)

ATSDR (**A**gency for **T**oxic **S**ubstances and **D**isease **R**egistry)

Conduct **Literature Searches** using databases to obtain historical and the most recent information; i.e. Toxline, Medline, Biosis, Cancerlit

Peer-reviewed scientific literature-available through Cornell libraries and interlibrary loans.

Technical Reports-NTIS-National Technical Information Service

TOXNET databases—EPA's IRIS database source of oncogenicity and regulatory status information

Grey literature—Studies submitted to EPA that are not published:

- Industry generated oncogenicity studies
- Some abstracts (short summaries) are on line (IRIS database)
- Request reports from industry
- Request reports from EPA through Freedom of Information Act

The critical evaluation will include some general background information, including chemical name, CAS#, trade name, history of use, and current regulatory status.

Evidence of cancer in other (non-breast) organ systems will be provided in synopsis form with some critical commentary, along with the current overall carcinogenicity classification by international (IARC) and US Federal Agencies (NTP, EPA).

Human epidemiological studies, animal studies, and other relevant studies on possible mechanisms of carcinogenesis are critically evaluated for evidence of exposure to agent and breast cancer risk based on "strength of evidence" approach, according to a modification of IARC criteria as listed in IARC Preamble. (See below for a more detailed explanation of the BCERF Breast Cancer Risk Classification scheme)

The **emphasis of the document** is the critical evaluation of the evidence for breast cancer carcinogenicity, classification of the agent's breast cancer risk, identification of research gaps, and recommendations for future studies. A section will also be devoted to brief summaries of new research studies that are in progress. A bibliography with all cited literature is included in each critical evaluation. Major international, federal and state agencies will be provided with copies of our report.

General Outline of BCERF Critical Evaluations

I. Chemical Information

- A. Common Name
- B. Chemical Name
- C. Chemical Formula
- D. Trade Names
- E. CAS # (Chemical Abstract Subject Number)
- F. Chemical Structure

II. History of Use

- 1. Date of first registration
- 2. Uses
- 3. Past usage / If available, current usage levels in US and NYS

III. Current Regulatory Status

- A. Current Regulatory Status, EPA
- B. Other sections as applicable

IV. Summary on Evidence of Overall Carcinogenicity (Non-Breast Sites)

- A. Human Studies
- B. Animal Studies
- C. Current Classification of Carcinogenicity by Other Agencies
 - 1. IARC (International Agency for Research on Cancer)
 - 2. NTP (National Toxicology Program)
 - 3. EPA (Environmental Protection Agency)

V. Critical Evaluation of the Scientific Evidence for Breast Carcinogenicity

- A. Human Studies will include:
 - 1. Case-Studies
 - 2. Human Epidemiological Cohort Studies
 - 3. Human Epidemiological Case-Control Studies
- B. Experimental Animal Studies
- C. Other Relevant Information, including mechanisms by which exposure may affect breast cancer risk (examples: co-carcinogenicity, estrogenicity, endocrine disruptor, mutagenicity, tumor promotion, cell proliferation, oncogene/tumor suppressor gene expression, immune function, etc.)

VI. Other Relevant Information

- A. Specific for the pesticide (i.e. may include information on environmental fate)
- B. When available will summarize information on detection/accumulation in human tissues / and validation of biomarkers

VII. Summary, Conclusions, Recommendation for Classification

VIII. Identification of Research Gaps, and Other Recommendations

IX. Brief Summaries of New Human Studies Currently Being Conducted

X. Bibliography

XI. Appendix A. Common Abbreviations, Acronyms and Symbols

XII. Appendix B. Critical Evaluations of Breast Cancer Risk

BCERF Breast Cancer Risk Classification Scheme (adapted from the IARC Preamble by S.M. Snedeker)

Group 1: **Human Breast carcinogen;** *sufficient evidence* of carcinogenicity to humans is necessary. *Sufficient evidence* is considered to be evidence that a **causal** relationship has been established between exposure to the agent and human breast cancer.

Group 2A: **Probable breast carcinogen;** this category generally includes agents for which there is 1) *limited evidence* of breast carcinogenicity in humans and *sufficient evidence* of mammary carcinogenicity in experimental animals. The classification may also be used when there is 2) *limited evidence* of breast carcinogenicity in humans and strong supporting evidence from other relevant data, or when there is 3) *sufficient evidence* of mammary carcinogenicity in experimental animals and strong supporting evidence from other relevant data.

Group 2B: **Possible breast carcinogen;** this category generally includes agents for which there is 1) *limited evidence* in humans in the absence of *sufficient evidence* in experimental animals; 2) *inadequate evidence* of carcinogenicity in humans or when human data is nonexistent but there is *sufficient evidence* of carcinogenicity in experimental animals, 3) *inadequate evidence* or no data in humans but with *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data.

Group 2C: **Potential to affect breast cancer risk;** this category includes agents for which there is **inadequate or nonexistent human and animal data**, but there is **supporting evidence from other relevant data** that identifies a mechanism by which the agent may affect breast cancer risk. Examples are, but are not limited to: evidence of agent's estrogenicity, disruption of estrogen metabolism resulting in potential to affect exposure to estrogen; evidence of breast tumor promotion, progression or co-carcinogenicity; increased expression of proto-oncogenes or oncogenes; evidence of inactivation of tumor suppressor gene associated with breast cancer; evidence of adverse effect on immune function; or evidence of a structural similarity to a known breast carcinogen (structure-activity relationship).

Group 3: **Not classifiable** as to its breast carcinogenicity to humans. Agents are placed in this category when they do not fall into any other group.

Group 4: **Probably not a breast carcinogen in humans:** This category is used for agents for which there is evidence suggesting a lack of breast carcinogenicity in human studies and in animal studies, together with a lack of related evidence which may predict breast cancer risk. The absence of studies does **not** constitute evidence for a lack of breast carcinogenicity.

Brief Definitions of Sufficient, Limited, and Inadequate Evidence (adapted for breast carcinogenicity from the IARC Preamble by S.M. Snedeker)

Human Studies

Sufficient evidence of carcinogenicity in humans: Must have established evidence between exposure to the agent and human breast cancer. Case-reports are given the least weight in considering carcinogenicity data in humans—they are suggestive of a relationship, but by themselves cannot demonstrate causality. Consistent, case-control studies which have controlled for confounding factors and have found high relative risks of developing breast cancer in relation to an identified exposure are given the most weight in determining a causal relationship.

Limited evidence of breast carcinogenicity in humans: A positive association has been observed between exposure to the agent and breast cancer, but chance, bias or confounding factors could not be ruled out.

Inadequate evidence of breast carcinogenicity in humans: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Experimental Animal Studies

Sufficient evidence of breast carcinogenicity in animals: Evidence of malignant tumors or combination of benign and malignant tumors in (a) two or more species of animals, (b) or two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Limited evidence of breast carcinogenicity in animals: The studies suggest a carcinogenic effect, but are limited for making a definitive evaluation because: (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent increases the incidence of only benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains of animals.

Inadequate evidence of breast carcinogenicity in animals: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.