DRAFT

For Review Only

Public Health Goal for SILVEX in Drinking Water

NOT A REGULATORY STANDARD

Prepared by

Pesticide and Environmental Toxicology Section
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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LIST OF CONTRIBUTORS

PREFACE

Drinking Water Public Health Goal of the Office of Environmental Health Hazard Assessment

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.

9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.

10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR SILVEX IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) proposes a Public Health Goal (PHG) of 25 ppb for silvex in drinking water, based on a NOAEL of 0.9 mg/kg-day for histopathologic changes in the livers of dogs fed silvex for two years (Mullison, 1966). Silvex [2-(2,4,5-trichlorophenoxy(propionic acid)] is a member of the class of herbicides known as chlorophenoxy acids, which includes 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). These compounds mimic the naturally occurring plant hormones called auxins, in that they stimulate plant cell growth, although the growth is often abnormal, leading to the death of the plant.

In 1986 all registrations of silvex and 2,4,5-T were cancelled by the United States Environmental Protection Agency (U.S. EPA). Both compounds were judged to pose unacceptable human health risks due to their contamination with the highly toxic byproduct of the production process, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Silvex was never registered in California.

Silvex adsorbs strongly to soil and biodegrades over a period of weeks to months. It is stable in water, from which it adsorbs strongly to sediment. Despite the ban on silvex use in the United States, according to a 1992 report (Gintautas *et al*., 1992) it continues to enter the environment through leachates from municipal landfills. Thus, it has the potential to enter the groundwater.

Silvex is readily absorbed from the digestive tract of humans and other mammals. It is efficiently excreted, primarily as the unchanged compound.

A limited database exists concerning the toxicity of silvex in mammals. The acute oral LD_{50}s range from 600 mg/kg in rats for the acid to 1410 mg/kg in mice for the propylene glycol butyl ether ester (U.S. EPA, 1987). Subchronic and chronic studies in rats and dogs indicate that the kidneys and liver are the most sensitive organs. The histopathologic changes in the livers of dogs used to set the chronic NOAEL of 0.9 mg/kg-day (Mullison, 1966) occurred at dose levels well below those causing developmental effects in rats and mice. Therefore, the PHG utilizes the NOAEL from the chronic dog study. Carcinogenicity studies in rats and mice were negative, although there were serious deficiencies in the study protocols. In addition, silvex was nonmutagenic in the Ames test.

The carcinogenicity of silvex in human populations has only been studied by association with other, more commonly used chlorophenoxy herbicides, i.e., 2,4-D and 2,4,5-T. Both case-control and cohort studies have been performed with workers exposed to these compounds. Results have been inconclusive, since about one-half the studies show no association while the other half show an association with certain rare cancers (soft tissue sarcoma and malignant lymphoma).

The California maximum contaminant level (MCL) for silvex in drinking water is currently set at 50 ppb. The federal MCL and maximum contaminant level goal (MCLG) are also set at 50 ppb. These regulatory levels are based on the adverse effects of silvex on the liver.

INTRODUCTION

Silvex is a hormonal herbicide belonging to the class of phenoxy herbicides, which includes 2,4-D and 2,4,5-T. The phenoxy herbicides mimic the natural plant hormones known as auxins. The herbicide is absorbed by the target plant, where it induces abnormal growth. This includes uneven cellular elongation and excessive tissue proliferation. As a consequence, vascular channels become disrupted and/or plugged. Death of the plant is likely to follow.

In 1979 the U.S. EPA placed restrictions on the use of silvex and 2,4,5-T (U.S. EPA 1979a). By 1985, all registrations of these herbicides in the U.S. were cancelled.

This proposed PHG for silvex was developed from the print literature and online information sources. The California Department of Pesticide Regulation (CDPR) has no studies on file for silvex, since it was never registered in California.

CHEMICAL PROFILE

Chemical Identity

Alternative common names for silvex are 2,4,5-TP and fenoprop. Discontinued trade names include Fruiton T, Kuron, AquaVex, Amchem 2,4,5-TP, Double Strength, Kurosal and Silvi-Rhap. The chemical formula for silvex is $C_9H_7Cl_3O_3$ and its structure is shown below in figure 1.

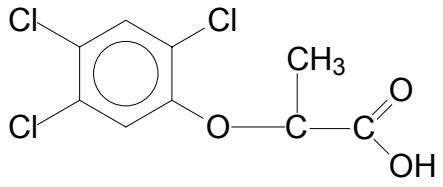


Figure 1. Silvex, or 2,4,5-trichlorophenoxypropionic acid

Physical and Chemical Properties of Silvex

Silvex is a solid at room temperature. It has a low solubility in water and a correspondingly high partition coefficient (Table 1). Its low volatility is shown by its low vapor pressure (Table 1). Despite its low solubility in water, it can still migrate in soil, especially clay and sandy soils.

Table 1. Properties of Silvex[1,2]

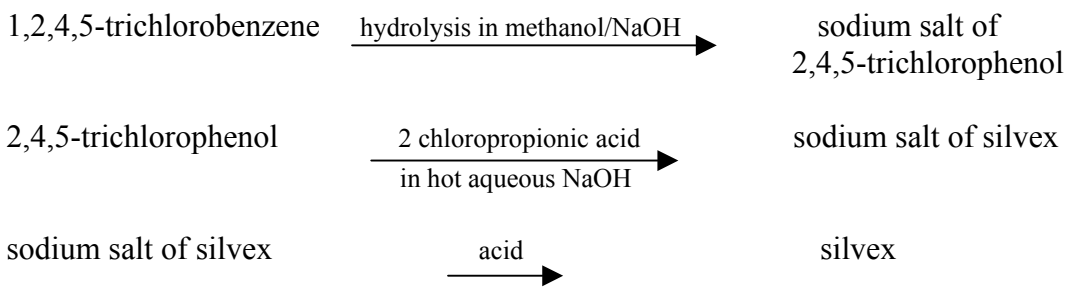
Property	Value or Information
Molecular weight[1]	269.51 ($C_9H_7Cl_3O_3$)
Physical state[1]	white powder
Melting point[1]	181.6 ^oC
Solubility[1]	water-140 ppm at 25 ^oC (0.5 mM) acetone-15.2% methanol-10.5%
Density[1]	1.2085 @ 20 ^oC
pKa[1]	2.84
Partition coefficient (octanol/water)[1]	log K_{ow} = 3.80
Vapor pressure[2]	6.46 x 10^{-6} @ 25 ^oC

[1]HSDB (2000b); [2]U.S. EPA (1985)

Production and Uses

Silvex was used primarily as a post-emergence herbicide for the control of woody plants and broadleaf herbaceous weeds in cropland, forests, and in bluegrass turf. It was also used for rangeland improvements, rights-of-way, and was effective in controlling aquatic weeds not susceptible to 2,4-D. In 1979, use of silvex and the closely related herbicide 2,4,5-T in forestry, rights-of-way, pasture and home/garden was suspended by the U.S. EPA. This action was in response to a reported increase in the spontaneous abortion rate experienced by women living in an area of western Oregon, where 2,4,5-T was used in forestry (see Toxicological Effects in Humans section below). Between 1979 and 1985, all other registrations for silvex and 2,4,5-T were cancelled. Only 360 kg of silvex were used in California in 1983 (IARC Monograph, 1986). From February 1985 to February 1986, existing stockpiles of these herbicides were allowed for highly limited use. Finally, by February 1986, all sales ceased.

Production of silvex in the United States peaked at approximately 3.7 to 4.1 x 10^6 pounds for the year 1976-77 (NAS, 1977). However, by the early 1980s, production was still at approximately 3 x 10^6 pounds/year (U.S. EPA, 1987b). Commercial synthesis of silvex is according to the following scheme:



If the temperature and pressure are not carefully controlled during the first step of synthesis, TCDD forms as a byproduct. By analogy with 2,4,5-T synthesis, older commercial samples of silvex could have contained as much as 30-50 ppm of contaminating TCDD (Ecobichon, 1996). This figure was reduced to less than 0.05 ppm by 1979 as a result of improved manufacturing methods (U.S. EPA, 1979b).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Today, the only expected human exposure to silvex is that resulting from its leaching from waste dump sites. Since silvex has a low vapor pressure, little volatilization of this leaching material would be expected. Silvex in the vapor phase reacts strongly with photochemically produced hydroxyl ions, leading to a relatively short half-life of 6.3 hrs (U.S. EPA, 2000).

Soil

Silvex adsorbs strongly to soil and biodegrades, although it can migrate in sandy and clay soils. Its half-life in soil is reported to be as short as 12-17 days (U.S. EPA, 2000) and as long as three to four months (Anonymous, 1988). Biodegradation produces 2,4,5-trichlorophenol.

Water

Silvex does not hydrolyze in water. It adsorbs strongly to sediment and biodegrades slowly. Compound near the water's surface is subject to photooxidation (U.S. EPA, 2000).

Prior to the final suspension of all sales of silvex in 1986, the herbicide was detected in surface water. From 1965 to 1968, silvex was measured in surface water of 15 western states (individual states not identified) at 0.01 to 0.21 ppb (NAS, 1977). In a 1973 publication, silvex was detected in 11/20 streams in the western United States (individual states not identified) at 0.01 to 0.14 ppb (HSDB, 2000b). In 1977, 12 rivers in the Ohio River valley were measured for pesticide contamination; silvex was detected in two of the rivers at 0.02 to 0.03 ppb (HSDB, 2000b). A study performed in 1992-96 as part of the National Water Quality Assessment Program

(NAWQA) analyzed 8200 samples of surface and groundwater from 20 major hydrologic basins (USGS, 2000). Three basins were located entirely within California (Sacramento River, San Joaquin-Tulare, Santa Ana) and one included a section of northeastern California and western Nevada (Nevada Basin and Range Study Unit). Six of 83 pesticides were not detected. One of the six was silvex, suggesting that the ban on silvex had effectively halted its entry into surface water.

Silvex contamination of groundwater has been minimal, as might be expected from its low propensity to migrate through most soils. In 1978 silvex was not detected in Nebraskan groundwater (detection limit = 0.005 ppb, HSDB, 2000b). A 1985 U.S. EPA report (Anonymous, 1988) measured silvex contamination of U.S. groundwater systems at less than 0.3 ppb, with most levels falling below 0.1 ppb (individual states not identified). The NAWQA study discussed above did not detect silvex in groundwater from 1992-96 (USGS, 2000). A study of drinking water wells in North Carolina, published in 1998, detected silvex in 1/41 wells at 0.1 ppb (Wade *et al*., 1998). No other California-specific data were located.

The recent low incidence of silvex detection in surface and groundwater is consistent with the cessation of silvex use. However, the herbicide continues to enter the environment via leachates from municipal landfills. Silvex was detected in leachates from 4/6 landfills located in six states (not including California) at 1-10 ppb, consistent with the levels expected from the disposal of household hazardous waste and plant material containing the herbicide (Gintautas *et al*., 1992). One of these landfills did not open until 1983, four years after the initial suspension of 2,4,5-T and silvex use by the U.S. EPA. The authors concluded that silvex retains the potential to enter the groundwater via these leachates.

Food

Tolerances for silvex in food, in effect prior to the banning of the herbicide, included 0.005 ppm in pears (post-harvest application) and 0.1 ppm in sugarcane, apples and plums (U.S. EPA, 1979b). An FDA market basket survey, covering the years 1965-68, detected silvex in 2/1548 food samples (Johnson, 1971). Both contaminated samples were reported as falling between 0.001 and 0.1 ppm. Silvex was detected in milk from dairy cows administered 1000 ppm in their feed for two to three weeks (Bjerke *et al*., 1972). The level of silvex in milk was 0.12 ppm.

By 1985, the FDA estimated that there was no longer any significant dietary exposure to silvex (U.S. EPA, 1985). This prediction was born out in a 1988-89 study, testing for 199 different pesticides in food samples from ten states (Minyard and Roberts, 1991). Silvex was not detected in any sample.

METABOLISM AND PHARMACOKINETICS

Absorption

Four male and four female Sprague-Dawley rats, administered ^{14}C-silvex by single-dose gavage at 5 mg/kg, excreted approximately 94 percent of the administered dose in their urine (78 percent) and feces (16 percent) by 192 hours (Sauerhoff *et al*., 1977a). A similar pattern of excretion was observed after intravenous dosing, suggesting that fecal excretion after oral administration was via bile. The authors concluded that an oral dose of silvex in rats was extensively, if not completely absorbed. A significant component was reabsorbed during enterohepatic circulation, as demonstrated by the more rapid excretion of silvex in bile duct-cannulated rats compared to bile duct-intact rats.

Human volunteers (seven males, one female) administered a single oral dose of silvex at 1.0 mg/kg achieved peak plasma levels within two to four hours of dosing, demonstrating rapid absorption (Sauerhoff *et al*., 1977b). Recovery in the urine and feces through 168 hours averaged approximately 80 percent ($\leq$ 3.2 percent in the feces), indicating that as in rats, humans absorb most if not all of an oral dose.

No data on silvex absorption through dermal contact or inhalation were located.

Distribution

Two male and two female Sprague-Dawley rats were administered ^{14}C-silvex by intravenous injection at 5 and 50 mg/kg. High dose animals exhibited the following tissue concentrations of labeled compound nine days after injection: liver 3.3 ppm, kidney 7.9 ppm, brain 0.14 ppm, perirenal fat 0.47 ppm, abdominal fat 1.47 ppm, and muscle 0.86 ppm. Values for low dose animals were at least 10-fold lower (Sauerhoff *et al*., 1977a).

Three cows or three beef calves were fed silvex at 300, 1000 and 2000 ppm for 28 days. Dose-dependent levels of silvex were measured in the kidney (11.5/14/25 ppm for 300/1000/2000 ppm in the feed), with decreasing concentrations measured in the liver, fat and muscle. Seven days after cessation of test article feeding, all tissue levels had dropped at least 10-fold. Sheep treated similarly accumulated about one-half the tissue levels of the calves (Leng, 1977).

Dairy cows fed silvex at 1000 ppm for two to three weeks achieved up to 0.12 ppm of the compound in their milk (Bjerke *et al*., 1972), while cows fed 5 ppm for six days had undetectable levels (St. John *et al*., 1964).

Metabolism

Esters of silvex are rapidly hydrolyzed in the animal gut, followed by rapid absorption. In man, silvex is excreted largely unchanged, or conjugated with glucuronic acid or amino acids (Leng, 1977). The basic structure is not readily

altered. For example, in cattle fed silvex, almost none was metabolized to 2,4,5-trichlorophenol, while in cattle fed 2,4,5-trichlorophenoxyacetic acid, high levels of the trichlorophenol were found. This suggests that the angular methyl group on the side chain of silvex prevents cleavage of the phenoxy ether linkage by rumen bacteria (Leng, 1977). Dairy cows fed silvex at 1000 ppm reached 0.12 ppm in their milk during feeding; however, no residues of 2,4,5-trichlorophenol were detected, further illustrating the stability of silvex in animals (Bjerke *et al*., 1972). Almost none of the ^{14}C-silvex administered to rats was measured as expired CO_2, indicating minimal degradation (Sauerhoff *et al*., 1977a).

Excretion

In humans administered a single oral dose of silvex at 1.0 mg/kg (Sauerhoff *et al*., 1977b), excretion in the urine followed first order kinetics, with a rapid initial phase (half-time of five hrs) and slower terminal phase (half-life of 26 hrs). By 24 hrs after administration, 65 percent of the dose was excreted in the urine as silvex and silvex conjugates, and 3.2 percent in the feces. By 168 hrs, on average 80 percent of the administered dose was excreted in the urine and feces.

In a rat study (Sauerhoff *et al*., 1977a), ^{14}C-silvex was administered by jugular cannula at 5 or 50 mg/kg. Excretion exhibited linear kinetics at 5 mg/kg, with 80 percent excreted in the urine and 14 percent in the feces by 192 hrs. In contrast, the kinetics of excretion were nonlinear at 50 mg/kg, with 69 percent of the administered dose excreted in the urine and 26 percent in the feces by 216 hrs. The pattern of excretion at the high dose level suggested that active transport in the kidney was saturated, indicating that low dose excretion data could not necessarily predict excretion at higher doses. Silvex excreted in the bile was subject to extensive enterohepatic circulation.

Silvex was detected in milk from dairy cows administered 1000 ppm in their feed for two to three weeks (Bjerke *et al*., 1972). The level of contamination in the milk, 0.12 ppm, declined rapidly after administration was halted.

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

Table 2 shows acute oral toxicity values for silvex in laboratory animals. Data on acute dermal toxicity, inhalation toxicity, primary eye irritation, and primary dermal irritation were not located.

Table 2. Summary of Acute Oral Toxicity of Silvex in Laboratory Animals

Species	Form of Silvex	LD_{50} mg/kg (95% CI)
Mouse	PGBE* esters	1410 (1000-2000)
Rat	Acid	650 (560-760)
Rat	Mixed butyl esters	600 (250-1000)
Rat	PGBE* esters	621 (473-814)
Guinea pig	PGBE* esters	1250 (500-2000)
Rabbit	Mixed butyl esters	750 (500-1000)
Rabbit	PGBE* esters	819 (610-1070)

* PGBE = propylene glycol butyl ether Reference: U.S. EPA, 1987a

Clinical signs of acute toxicity include depression, muscular weakness, anorexia, weight loss, paresthesia, ataxia, peripheral neuropathy and posterior paralysis. Lesions have been generally unremarkable, and include mild damage to the liver and kidney, and inflammation of the gastrointestinal tract (Gehring and Betso, 1978). It has been suggested that acute toxicity from silvex could result from internal hemorrhage caused by the inhibition of platelet aggregation (Elo *et al*., 1991).

Acute administration of silvex also causes cellular changes, including peroxisome proliferation in mouse liver (Voskoboinik *et al*., 1997) and induction of microsomal P-450 mixed-function oxidase in rat liver (Bacher and Gibson, 1988).

Subchronic Toxicity

Twenty rats/group were fed the propylene glycol butyl ether ester of silvex (Kuron) at 0, 10, 30, 100, 300 and 600 mg/kg-day for 90 days (Mullison, 1966). No clinical signs were observed and necropsies at 90 days were normal, except for slight enlargement of the liver (no histopathologic correlates, dose groups affected not indicated). There were no changes in the blood (hemoglobin concentration, erythrocytes or leukocytes) or urine (reducing substances, albumin, microscopic elements). Body weights of males and females fed 300 or 600 mg/kg-day were significantly lower than controls. The high dose animals had histopathologic changes indicative of malnutrition. A NOAEL of 10 mg/kg-day was selected.

Another 90 day feeding study in rats (numbers of animals/dosage group not indicated, Mullison, 1966) utilized the sodium salt of silvex at 0, 100, 300, 1000, 3000 and 10000 ppm in the feed, corresponding to an intake in high dose animals of approximately 300 mg/kg-day (Dost, 1978). High dose animals would not eat the food for more than a few weeks, so this dosage group was discontinued. In males, growth was retarded at all concentrations except the lowest, while female growth was only inhibited at the highest concentration (3000 ppm). Liver sizes were increased in males at $\geq$ 300 ppm and in females at $\geq$ 100 ppm. Kidney sizes were increased in males at $\geq$ 100 ppm and in females at $\geq$ 1000 ppm. Histopathologic changes observed at all dose levels included: 1) swelling, granular degeneration and

necrosis of hepatocytes, 2) swelling of renal tubule cells, 3) vacuolation and degeneration of seminiferous tubules (Dost, 1978). Hematology was normal.

Two beagle dogs/sex/dose level were fed Kurosal (potassium salt of silvex) for 90 days at 0, 100, 300 and 1000 ppm, yielding test article intakes of 0, 4, 13 and 40 mg/kg-day (Mullison, 1966). Both high dose females had lower body weights relative to controls. One female suffered pathological changes to the liver, while the other animal had increased serum alkaline phosphatase, decreased hemoglobin, and decreased hematocrit. No effects were observed at lower doses, giving a NOAEL of 13 mg/kg-day.

In a U.S. Department of Agriculture (USDA) study, three sheep/sex were administered the propylene glycol butyl ether ester of silvex (Kuron) at 100 mg/kg-day by oral gavage for 21 days, followed by ten days at 150 mg/kg-day (Wright *et al*., 1966). Two animals died, one after 29 doses and one after 31 doses. Prior to death, the animals exhibited anorexia, depression, tense appearance and muscular spasms. At necropsy, the animals that died had inflamed and swollen lymphatics, enteritis, enlarged and congested spleen, and rumen stasis, along with elevated serum levels of glutamic oxaloacetic transaminase and lactic dehydrogenase.

Genetic Toxicity

The mutagenicity of silvex has been tested in two studies measuring reversion to autotrophy in histidine-requiring mutants of *S. typhimurium* (Ames test). Both in the absence (Andersen *et al*., 1972) and presence (Mersch-Sundermann *et al*., 1988) of an activating S9 microsomal fraction, silvex was nonmutagenic.

Developmental and Reproductive Toxicity

The developmental and reproductive effects of silvex have been studied to a limited extent. A single dose level of 404 mg/kg-day was tested in CD-1 mice by both oral and subcutaneous administration during gestation days 12-15 (Courtney, 1977). Maternal effects included increased weight gain, probably due to increased liver size. Subcutaneous administration caused increased fetal mortality relative to controls ($p = 0.01$). Both oral and subcutaneous administration resulted in decreased fetal weight relative to controls ($p = 0.01$). Oral administration produced cleft palate in 7 percent of the fetuses, compared to 3 percent following subcutaneous administration and 0 percent in controls. In other unpublished studies in mice, lower dose levels administered during gestation caused minor skeletal variations at 50 mg/kg-day, with no effects at 25-35 mg/kg-day (Milby *et al*., 1981).

Silvex containing less than 0.05 ppm TCDD was administered to rats during gestation days 6-15 at 25 to 100 mg/kg-day (U.S. EPA, 1979b). Maternal effects included alopecia, loss of appetite and vaginal bleeding (dose levels not indicated). Skeletal abnormalities were cleft palate, retarded ossification, extra cervical ribs, microphthalmia and cardiovascular changes (dose levels not indicated). Increased

fetotoxicity was observed at 50 mg/kg-day. The NOAEL was probably 25 mg/kg-day (U.S. EPA, 1979b).

Immunotoxicity

No data were located.

Neurotoxicity

No data were located.

Chronic Toxicity/Carcinogenicity

Innes *et al*. (1969) tested the tumorigenic potential of silvex in two hybrid strains of mice. Eighteen mice/sex/strain were administered silvex by oral gavage at the MTD of 46.4 mg/kg-day starting at age seven days until age 28 days, followed by administration in the feed at a concentration (121 ppm) calculated to maintain the MTD until necropsy at age 18 months. Four groupings of tumor types were evaluated: hepatomas, pulmonary tumors, lymphomas and total mice with tumors. Silvex did not increase the incidence of any tumor type or the total number of mice with tumors ($p = 0.01$). This study suffers from the shortcomings of too few animals, a less-than-lifetime exposure, and only a single dosage level.

Twenty five rats/sex/dose level were administered the potassium salt of silvex (Kurosal) in their feed for two years at 0, 10, 30, 100 and 300 ppm (Mullison, 1966). The high dose animals exhibited slightly lower growth rates and slightly increased relative kidney weights without accompanying gross pathological findings. The NOAEL was 100 ppm, corresponding to a daily intake of 2.6 mg of silvex acid/kg. As a test for carcinogenicity, this study has two serious deficiencies: no evidence that a maximum tolerated dose (MTD) was achieved, and low number of animals per group.

A two-year feeding study was performed with the potassium salt of silvex (Kurosal) in four beagle dogs/sex/dose level at 0, 56, 190 and 560 ppm (Mullison, 1966). Pathological effects were observed in the livers of males at 190 and 560 ppm and in females at 560 ppm. No other details of the pathology were provided in the publication by Mullison (1966). In a later publication, the liver changes observed in the Mullison (1966) study were described as “mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation” (Gehring and Betso, 1978). The NOAELs were 56 ppm for males and 190 ppm for females, corresponding to 0.9 and 2.6 mg of silvex acid/kg-day, respectively.

The shortcomings of the above rodent studies notwithstanding, these results provide no evidence to suggest that silvex is tumorigenic in rats or mice. The chronic NOAEL of 2.6 mg of silvex acid/kg-day in rats and female dogs agrees well with that in male dogs (0.9 mg of silvex acid/kg-day). The slightly higher susceptibility

of male dogs may result from less efficient excretion of organic acids (Gehring and Betso, 1978).

Toxicological Effects in Humans

A single study has been reported in which seven male and one female human volunteers were administered a single dose of silvex at 1 mg/kg (Sauerhoff *et al*., 1977b). No effects were observed on any toxicologic parameter including clinical chemistry, hematology and urinalysis.

The original U.S. EPA decision to restrict the use of silvex was in response to a reported increase in miscarriages experienced by women living in a forested area of western Oregon, where the chlorophenoxy herbicide 2,4,5-T was regularly sprayed (U.S. EPA, 1979a). This herbicide is closely related to silvex with regard to both chemical structure and contamination by TCDD. Not only was the spontaneous abortion rate higher in the sprayed area compared to urban and forested areas considered unexposed, but the miscarriages peaked in June and July, shortly after the peak of springtime herbicide application in March and April (see Table 3 below). These human health effects were suspected to have resulted from exposure to contaminating TCDD, rather than exposure to 2,4,5-T (Smith, 1979; U.S. EPA, 1979a).

Table 3. Spontaneous Abortion Index in Study Area Sprayed with 2,4,5-T During 1972-1977

Test Area	Average monthly spontaneous abortion index*	Index during June and July
Study area	80.8	130.4
Urban control area	43.8	44.9
Forest control area	65.4	46.0

*Abortion index for 1972-1977 = spontaneous abortions per 1000 births related to the month of conception for miscarriage terms of up to about 20 weeks. Reference: U.S. EPA, 1979a.

Subsequent epidemiological studies have focused on the association between phenoxy herbicides and two rare cancers, soft tissue sarcoma (STS) and malignant lymphoma (ML). In most of the studies, exposure was to 2,4-D and/or 2,4,5-T, with exposure to silvex being much less frequent. Unfortunately, whether comparing case-control (nine studies) or cohort (14 studies) studies the results are inconclusive, since the number of studies indicating an association between phenoxy herbicides and STS or ML was similar to the number indicating no association. This situation may improve as the lengths of follow up increase.

A study of production workers at a plant manufacturing 2,4-D and 2,4,5-T detected slower nerve conductance in exposed workers compared to controls (Singer *et al*., 1982). The sural nerve showed the biggest effect: 34.0 versus 40.1 m/sec in exposed

workers versus controls ($p < 0.02$). It has been suggested that phenoxy acid herbicide-induced neurological toxicity could be the basis for the increased risk of suicide (Standardized Mortality Ratio = 210, $p = 0.04$) observed in a cohort of forestry workers (Green, 1991).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The chronic studies described above yielded the most sensitive endpoints for silvex toxicity: increased kidney size in the rat (NOAEL = 2.6 mg/kg-day; Mullison, 1966) and histopathologic changes to the livers of male dogs (NOAEL = 0.9 mg/kg-day; Mullison, 1966). No other changes were described in the chronic dog study (Mullison, 1966). In a later publication, the liver changes to dogs in the Mullison (1966) study were described as "mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation" (Gehring and Betso, 1978). These chronic results are in good agreement with the endpoints and dose levels of the subchronic toxicity studies described above: histopathologic changes to the liver, kidneys and seminiferous tubules of rats (LOEL = 3.0 mg/kg-day; Dost, 1978) and liver pathology along with reduced body weights in dogs (NOAEL = 13 mg/kg-day; Mullison, 1966). The teratogenicity/reproductive toxicology studies defined higher NOAELs than the subchronic and chronic studies: 25 mg/kg-day in both rats (based on fetotoxicity and developmental effects) and mice (based on skeletal variations). Therefore, the lowest NOAEL of 0.9 mg/kg-day from the chronic study in dogs (Mullison, 1966) was chosen for calculation of the proposed PHG.

Carcinogenic Effects

The U.S. EPA has designated silvex as a Group D carcinogen; i.e., not classified with regard to carcinogenicity due to lack of human data and inadequate animal testing. In the studies described above, silvex was nontumorigenic in rats (Mullison, 1966) and mice (Innes *et al*., 1969). The rodent studies have serious shortcomings including too few animals, no evidence of an MTD (rat study) and inclusion of only a single dose level (mouse study). Nonetheless, these data, along with the studies showing a lack of genotoxicity, do not suggest that silvex is carcinogenic.

CALCULATION OF PHG

Noncarcinogenic Effects

The equation for calculation of a public health-protective concentration (C, in mg/L) of silvex in drinking water is:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL = no-observed-adverse-effect-level of 0.9 mg/kg-day based on histopathologic changes to the livers of dogs (Mullison, 1966)

BW = adult bodyweight (a default of 70 kg for males);

RSC = relative source contribution of 80 percent (0.80);

UF = uncertainty factor of 1000;

L/day = volume of daily water consumption of an adult (2 L/day).

The NOAEL of 0.9 mg/kg-day is from the chronic dog study (Mullison, 1966), where pathological liver changes were observed in males fed silvex at the next highest dose level of 2.6 mg/kg-day. An RSC value of 80 percent (0.80) was chosen because any significant human exposure to silvex is expected to occur through drinking water, as a result of material leaching from waste dump sites and entering the groundwater (Gintautas *et al*., 1992). Other routes of exposure such as food or air are unlikely, because silvex use was banned in this country approximately 15 years ago.

An uncertainty factor of 1000 is used for the calculation. This includes a default factor of ten for variability within the human population, a default factor of ten for extrapolation from dogs to humans, and another factor of ten for numerous study deficiencies and data gaps.

Absorption of silvex through dermal contact with drinking water, such as during bathing, is not expected to be significant. This conclusion is based on dermal absorption of 2,4,5-T (HSDB, 2000a), a structurally related herbicide with properties similar to those of silvex. In addition, absorption by secondary inhalation during household water use is unlikely, due to the low volatility of silvex. Therefore, significant exposure to silvex is considered to occur only through ingestion of drinking water, and the standard value of 2 L/day is used.

Therefore,

$$C = \frac{0.9\ mg/kg\text{-}day \times 70\ kg \times 0.8}{1000 \times 2\ L/day} = \mathbf{0.0250\ mg/L} = \mathbf{25\ ppb}$$

Based on the above, a PHG of 25 ppb is proposed for silvex in drinking water.

RISK CHARACTERIZATION

The NOAEL used to calculate the proposed PHG is taken from the chronic feeding study in dogs (Mullison, 1966), and is based on histological changes to the liver at

2.6 mg/kg-day. No other details of the pathology were provided in the Mullison (1966) publication. A later publication described the liver changes observed in the Mullison (1966) study as "mild degeneration and necrosis of hepatocytes with slight fibroblastic proliferation" (Gehring and Betso, 1978). Similar pathological alterations to hepatocytes were observed in rats dosed at 3.0 mg/kg-day (LOAEL) for 90 days (Dost, 1978). Thus, there is agreement in these two species that similar levels of silvex cause hepatocyte damage. The mechanism by which this occurs is not known.

The endpoint of hepatocyte degeneration and necrosis has not been evaluated in chronically exposed humans. Thus, it is not known if hepatocytes in humans are more or less sensitive to this chemical than those in dogs. Therefore, use of a 10-fold uncertainty factor for extrapolation from dogs to humans is appropriate.

Use of a default 10-fold uncertainty factor for variability in sensitivity to silvex within the human population (including the sensitivity of children) is also appropriate, since this potential variable has not been studied. Although this pesticide was cancelled due to reports of increased human miscarriage rates from a related phenoxy herbicide, the available animal reproductive data for silvex do not support the presumption of a particular sensitivity of reproductive parameters (i.e., much lower NOAELs than for the critical effect on hepatocytes).

An uncertainty factor of 10-fold has been added to account for numerous study deficiencies and data gaps. As mentioned above and in the following paragraph, the oncogenicity studies in rats and mice had serious deficiencies. For developmental toxicity, the mouse study included only a single dose level, while the report of the rat study did not clearly indicate the study NOAEL. No reproductive toxicity study was located. In addition, genetic toxicity testing was limited to reverse mutation in bacteria.

The decision to calculate a proposed PHG based on noncarcinogenic endpoints is primarily based on the failure of silvex to produce tumors in rodents. As discussed above, the two-year rat study is deficient in that an MTD was not achieved and low numbers of animals were used per dosage group (Mullison, 1966). The 18-month mouse study also utilized too few animals and contained only a single dosage group (Innes *et al*., 1969). Nonetheless, the absence of tumors in the rodent studies along with the absence of mutagenicity in the Ames test (Andersen *et al*., 1972; Mersch-Sundermann *et al*., 1988), do not support the use of a carcinogenic endpoint for calculation of the proposed PHG. The closely related chlorophenoxy herbicides 2,4-D and 2,4,5-T, as well as the precursor for silvex synthesis, 2,4,5-trichlorophenol, were not shown to be carcinogenic in laboratory animals nor mutagenic both *in vitro* and *in vivo*..

The epidemiology of exposure to chlorophenoxy herbicides primarily deals with 2,4-D and 2,4,5-T, with exposure to silvex being much less frequent. Of 14 cohort studies surveyed, two studies found a statistically significant association between herbicide exposure and non-Hodgkin's lymphoma (Zahm and Blair, 1992; Becher *et al*., 1996), one study detected an association with soft tissue sarcoma (Saracci *et al*., 1991), and one study measured a general increase in tumor incidence (Axelson *et al*.,

1980). Ten studies found no significant associations (Poland *et al*., 1971; Riihimaki *et al*., 1983; Green, 1987; Ott *et al*., 1987; Bond *et al*., 1988; Bond *et al*., 1989; Johnson, 1990; Green, 1991; Kogevinas *et al*., 1997; Fleming *et al*., 1999). Of nine case-control studies, two showed a statistically significant correlation between exposure and soft tissue sarcoma (Hardell and Sandstrom, 1979; Eriksson *et al*., 1981), while a third showed an association with malignant lymphoma (Hardell *et al*., 1981). The other six case-control studies involving soft tissue sarcoma (Smith *et al*., 1984; Bond *et al*., 1989; Johnson, 1990; Smith and Christophers, 1992), non-Hodgkin's lymphoma (Pearce *et al*., 1986; Bond *et al*., 1989; Cantor *et al*., 1992) and malignant lymphoma (Johnson, 1990; Smith and Christophers, 1992) measured no statistically significant associations between exposure to chlorophenoxy herbicides and the indicated malignancy. These inconclusive results may change as the times from exposure until the onset of cancer increase, as the studies are updated.

Silvex was originally banned due to its contamination with TCDD (see "Toxicologic Effects in Humans" section above). At the time of the EPA's decision to suspend silvex use in 1979, contaminating levels of TCDD in eight samples of silvex ranged from 0.012-0.024 ppm (PMEP, 2000). At these low levels, toxicity from silvex administration to laboratory animals is due to the silvex molecule rather than TCDD (Anonymous, 1977; Green and Cohen, 1982). This conclusion is supported by an oral LD_{50} comparison in rats: 650 mg/kg for the silvex acid (see Table 2) versus 22-45 µg/kg for TCDD (HSDB, 2000c). In addition, TCDD does not leach from soil or move through soil (HSDB, 2000c), making it unlikely that it would leach from landfills along with silvex (Gintautas *et al*., 1992). Therefore, it is unlikely that today's low level of human exposure to silvex would be accompanied by exposure to TCDD.

OTHER REGULATORY STANDARDS

The U.S. EPA, based on the same chronic study used for developing the proposed PHG (Mullison, 1966), derived a lifetime health advisory (HA) and Recommended Maximum Contaminant Level (RMCL) for silvex in drinking water of 0.052 mg/L. This calculation assumed a daily drinking water intake of two L/day and an RSC of 20 percent (U.S. EPA, 1987; Anonymous, 1988). The MCL and MCLG of 50 ppb were based on this calculation (U.S. EPA, 2002). The proposed PHG developed here is different than the U.S. EPA's MCL for three reasons. First, an RSC of 0.80 (rather than 0.20) is used for the PHG, since future human exposure to silvex is expected to occur primarily through drinking water. When the MCL was established, other routes of human exposure may have been considered likely, since the ban on silvex had only been in place for a few years. Second, the NOAEL of 0.9 mg/kg-day used in this proposed PHG is taken directly from the chronic dog study reported in the publication by Mullison (1966), rather than the value of 0.75 mg/kg-day used by the U.S. EPA (1987), based on their standard assumption of food consumption per ppm of diet (U.S. EPA, 2001). Since the dog study was performed in the author's laboratory at Dow Chemical, and included measurements of food consumption, we chose Mullison's (1966) estimates of test article consumption rather than those

calculated by the U.S. EPA using their standard assumption of food consumption by dogs. Lastly, as described above in the Risk Characterization section, an uncertainty factor of 10 was added due to numerous study deficiencies and data gaps.

Using the same chronic dog study, the National Academy of Sciences calculated an Acceptable Daily Intake (ADI) of 0.00075 mg/kg-day based on a NOAEL of 0.75 mg/kg-day and an uncertainty factor of 1000 (NAS, 1977). The use of an uncertainty factor of 1000 probably includes a factor of 10 for database deficiencies, although this was not explicitly stated in the publication. From this ADI they derived a suggested no-adverse-effect level in drinking water of 0.00525 mg/L. This value is almost 5-fold lower than the proposed PHG, and reflects the use of an RSC for drinking water of 20 percent rather than 80 percent, and a slightly lower NOAEL for the Mullison (1966) study of 0.75 mg/kg-day rather than 0.9 mg/kg-day.

The California Department of Health Services Web site lists an MCL for silvex in drinking water of 0.05 mg/L. Other states' drinking water standards include New York at 0.010 mg/L, Arizona at 0.052 mg/L, Maine at 0.001 mg/L, Minnesota at 0.060 mg/L (HSDB, 2000b) and North Carolina at 0.050 mg/L (Wade *et al*., 1998). The values for California, Arizona, Minnesota and North Carolina are essentially the same as the U.S. EPA MCL.

The Guidelines for Canadian Drinking Water Quality 1978 (Toxline, 2000) give a maximum acceptable concentration for silvex of 0.01 mg/L, based on an RSC of 20 percent, an ADI of 0.002 mg/kg-day, and a drinking water consumption of 2 L/day. This ADI of 0.002 is approximately 2-fold greater than that calculated in the proposed PHG (0.0009 mg/kg-day), and may reflect Health Canada's use of a 500-fold uncertainty factor, rather than the 1000-fold factor used in the proposed PHG. The 1999 Canadian guidelines do not specify a regulatory level for silvex in drinking water, since it was no longer registered in Canada (Health Canada, 2000).

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