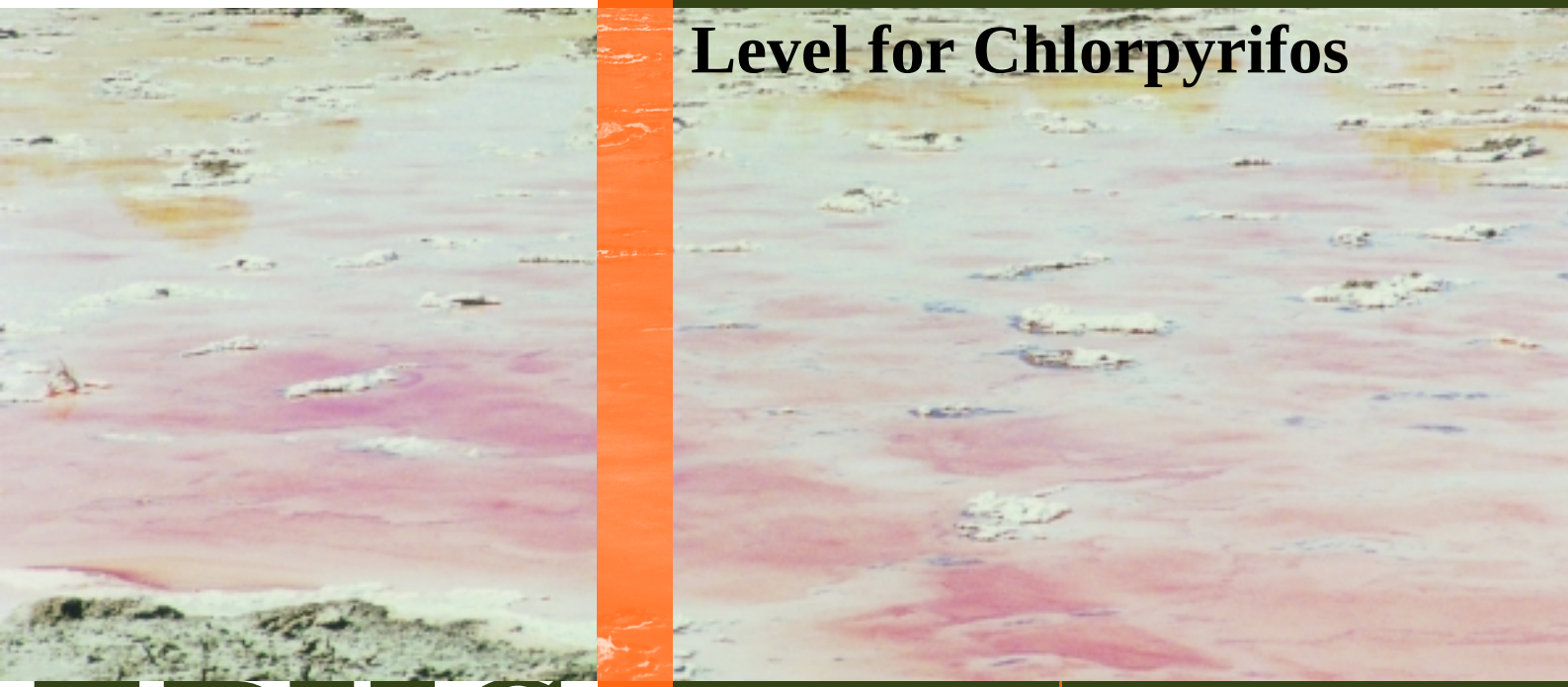
# Health-Based Investigation Level for Chlorpyrifos



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# Health-Based Investigation Level for Chlorpyrifos

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## 1 INTRODUCTION

Chlorpyrifos [O,O-diethyl O-(3,5,6-trichloro-2-pyrdinyl)-phosphorothioate] is a moderately toxic, broad-spectrum chlorinated organophosphate insecticide. Chlorpyrifos has been used extensively for the past 30 years in Australia to control numerous soil and foliar pests of crops in agriculture (mainly horticulture) and indoor and outdoor pests in household settings. Chlorpyrifos is known by a variety of trade names such as Durban, Lorsban, Agromil, Bullet, Chlofos, Destroyer, Dhanwan, Dorson, Omexan, and Panda (not an exhaustive list). In Australia there are 164 registered products containing chlorpyrifos and the annual use is about 1000 tonnes (NRA, 2000). It is currently included in Schedule 6 of the Standard for the Uniform Scheduling Drugs and Poisons (SUSDP) but concentrations of 5% or less are in Schedule 5 (as at August 2000).

The toxicity of chlorpyrifos has been reviewed by several organisations including the Agency for Toxic Substances and Disease Registry (ATSDR), US Environmental Protection Agency (EPA), National Registration Authority (NRA) and the National Drugs and Poisons Schedule Committee (NDPSC) over a number of years. The NDPSC most recently reviewed its scheduling of chlorpyrifos in August 2000 as it was identified as a candidate for priority review under the NRA's Existing Chemical Review Program (ECRP) in 2000. The NDPSC reviewed its scheduling in light of a paper by Zheng *et al*. (2000) which identified a difference in the $LD_{50}$ between neonatal, juvenile and adult rats. The NRA Board selected chlorpyrifos for review because of concerns regarding its very high toxicity to birds; water pollution potential and US restrictions imposed to reduce hazards to fish, birds and other wildlife; demonstrated potential for adverse effects in users; and high potential for chronic and moderate potential for acute toxicity risk. The NRA review is the major document used in the derivation of the health based soil guideline for chlorpyrifos in this paper.

## 2 PROPERTIES AND ENVIRONMENTAL BEHAVIOUR

### 2.1 PHYSICAL AND CHEMICAL PROPERTIES

Chlorpyrifos is a white crystalline solid at room temperature that has a mild mercaptan odour. It is a lipophilic chemical with an octanol-water partition coefficient (Log $K_{ow}$) of 4.70 and it is practically insoluble in water but is soluble in most organic solvents (Hummel and Crummet, 1964). It is stable in neutral and acidic aqueous solutions but its stability decreases with increasing pH. Additional information is summarised below (NRA, 2000).

| | |
|---|---|
| Empirical formula | $C_9H_{11}Cl_3NO_3PS$ |
| Molecular weight | 350.6 |
| Solubility in Water (25°C) mg/L | 1.4 |
| Partition coefficient (Log $K_{ow}$) | 4.70 |
| Vapour Pressure (25°C) mPa | 2.7 |

## 2.2 CHLORPYRIFOS IN THE ENVIRONMENT

Chlorpyrifos is used extensively in Australia. It is used as an agricultural pesticide, pre- and post-construction termiticide and as a household insecticide. Many formulations are available in Australia including emulsifiable concentrate, wettable powder, ultra low volume, microencapsulate, seed dressing, granule, prepared bait and sustained release formulations. There are also some animal health products registered.

## 2.3 SOIL ABSORPTION AND MOBILITY

The physical and chemical characteristics, which influence the fate and transport of chlorpyrifos in the environment are its low solubility, volatility, and strong affinity for small particulate matter. Chlorpyrifos exists in the atmosphere primarily in the vapour phase, but can partition to particulates. Chlorpyrifos is not persistent in water, due to volatilisation and strong adsorption to particulate matter.

Chlorpyrifos dispersion to the atmosphere following application may release it to sediment/soil where slow/moderate degradation occurs. The persistence in soil depends on the soil properties/type and the environmental conditions. Environmental factors that affect the degradation of chlorpyrifos include photolysis, moisture content, microorganism availability and temperature. It is accepted that chlorpyrifos has low to no mobility in soil based on the soil/water partition coefficient (KoC) values of 995-31000 that have been reported in a variety of soils (Racke, 1993). Sandy and moist soils appear to enhance airborne concentrations (Vaccarco, 1993; Racke, 1993).

In neutral to acid soils, chlorpyrifos' half-life ranges from 92 to 341 days; with increasingly alkaline soils this half-life decreases to 11-200 days. These faster rates in alkaline soils are thought to reflect increased catalysation by metal ions or bacterial soil enzymes. Studies on the effects of sterilisation on soil degradation of chlorpyrifos indicate that the rate in non-sterile soil was significantly faster than in sterilised soil, suggesting that biodegradation is a significant pathway. Degradation is also decreased at lower temperatures and varies with moisture content (Schimmel *et al*., 1983).

## 2.4 BIOACCUMULATION OF CHLORPYRIFOS

Chlorpyrifos bioaccumulates in moderate to high levels in fish and other aquatic life. Measured bioconcentration factors (BCF) in fish suggest bioconcentration in aquatic organisms is high, with a BCF of 1400 in rainbow trout and 745 in oysters reported (NRA, 2000). However, residues rapidly dissipate in clean water, with typical half-life of two days, due to volatilisation and strong adsorption to particulate matter.

# 3 EXPOSURE STANDARDS

## 3.1 ENVIRONMENTAL STANDARDS

The Agriculture and Resource Management Council of Australia and New Zealand and National Health and Medical Research Council (ARMCANZ/NHMRC) have set a drinking water health guideline value of 0.01 mg/L (ARMCANZ/NHMRC, 1996). This value was derived using 10% of the Acceptable Daily Intake (ADI) set by Joint FAO/WHO Meeting on Pesticide Residues (JMPR) (0.001 mg/kg/day) as the Australian ADI had not been published at the time.

## 3.2 OCCUPATIONAL EXPOSURE

The National Occupational Health and Safety Commission (NOSCH) has set an occupational guideline of 0.2 mg/m$^3$ (TWA).

## 3.3 OTHER RELEVANT GUIDELINES AND REGULATIONS

| Organisation | Regulatory value | Dose |
|---|---|---|
| Therapeutic Goods Administration | ADI | 0.003 mg/kg/day |
| JMPR | ADI | 0.001 mg/kg/day |
| US EPA | Reference Dose (RfD) | 0.003 mg/kg/day |
| US EPA Region 9 | Preliminary Remediation Goal (PRG) for soil | 180 mg/kg |
| US EPA Region 9 | PRG for tap water | 1.1 µg/L |
| US EPA Region 9 | PRG for ambient air | 110 µg/m$^3$ |

# 4 TOXICOKINETICS

## 4.1 ABSORPTION, METABOLISM, DISTRIBUTION AND EXCRETION

Chlorpyrifos is moderately fat-soluble and is absorbed through the skin, gastrointestinal tract and the lungs. Dermal absorption through undamaged skin is relatively low in humans (between 1-3% of applied dose), but increases at higher temperatures and in the presence of dermatitis (Nolan *et al*., 1982 as cited in NRA, 2000). Approximately 70% is absorbed after oral administration in humans (Nolan *et al*., 1983 as cited in NRA, 2000). There are no studies on the absorption of chlorpyrifos following inhalation, but bioavailability is expected to be high.

After oral administration in rats, chlorpyrifos is widely distributed in the body but accumulates in the fat. Elimination from fat is slower ($t_{½}$ = 62 h) than elimination from other tissues ($t_{½}$ for liver, kidney and heart is about 10-16 h) (Smith *et al*., 1967). In dermally exposed goats and mice a similar pattern was observed (Smith *et al*., 1967).

Chlorpyrifos is bioactivated in the liver to chlorpyrifos-oxon by cytochrome P-450-dependent desulfuration. This oxon is then rapidly hydrolysed to 3,5,6-trichloro-2-pyridinol (TCP) via micosomal esterase, which includes paraoxanase and chlorpyrifos oxonase, or via a non-enzymatic process. Alternatively, chlorpyrifos is dearylated to form diethyl thiophosphoric acids and TCP in a reaction catalysed by microsomal enzymes.

The chlorpyrifos oxon is able to bind irreversibly to acetylcholinesterase (AChE) thus inhibiting its activity. The affinity for the chlorpyrifos oxon is greater for plasma and hepatic esterases than for AChE which represents a significant detoxification mechanism because it prevents much hepatically generated chlorpyrifos oxon from entering the general circulation and target tissues (Storm, 2001). These enzymes are found in the plasma and liver and hydrolyse a large number of organophosphorus compounds by cleaving the phosphoester, anhydride, P-F or P-CN bonds. The bioactivation and subsequent detoxification must occur rapidly as the chlorpyrifos-oxon is not detected in the excretory products or clinical chemistry parameters in most animal experiments. High rates of hepatic dearylation and esterase binding may provide a protective factor but it should be recognised that chlorpyrifos can be activated in other tissues of the body such as the brain, and that there is genetic polymorphism for paraoxanase as displayed in human serum (Smith, 2001).

TCP is the principal metabolite detected (Nolan *et al*., 1984). The bulk of bioactivation takes place in the liver, while detoxification takes place in the liver and plasma. TCP has insignificant anti-cholinesterase activity and is not regarded as toxicologically important, whereas chlorpyrifos-oxon is a potent cholinesterase inhibitor.

Chlorpyrifos metabolites are rapidly excreted in the urine and faeces. Urinary excretion is primarily in the form of TCP conjugates. An elimination half-life of 27 h has been established following oral or dermal exposure (Nolan *et al*., 1984). Studies in humans suggest that more than 90% of administered chlorpyrifos is rapidly excreted with small amounts being deposited in the fat and fatty tissues (Nolan *et al*., 1984).

## 5 TOXICOLOGY

### 5.1 ACUTE TOXICITY

The typical signs of acute toxicity of chlorpyrifos are consistent with AChE inhibition, including increased swallowing, excessive salivation, rapid breathing, twitching and rapid contractions of muscles, coarse and generalised body tremors, lacrimation, urination, defecation, depression, prostration, epileptoid tremors, convulsions, respiratory failure and death. Recovery in surviving animals is usually evident within one week after dosing. Chlorpyrifos is a slight eye and skin irritant in rabbits.

Significant inhibition of plasma and red blood cell (RBC) cholinesterase (ChE) is the most sensitive effect in animal and human studies regardless of exposure duration. These are the most commonly used toxicological endpoints. RBC and plasma ChE depression is observed at much lower doses than doses that inhibit brain ChE or cause clinical signs of toxicity.

The acute toxicity of chlorpyrifos following oral exposure is moderate, with $LD_{50}$ values ≥ 96 mg/kg in rats, ≥ 102 mg/kg in mice and ≥ 1580 mg/kg in rabbits, whereas it is low after dermal exposure ($LD_{50}$ ≥ 2000 mg/kg in rats and ≥ 1233.57 mg/kg in rabbits) (NRA, 2000).

Effects on the respiratory, musculoskeletal, gastrointestinal, dermal, urinary and cardiovascular system observed in a number of animal and human studies were all consistent with ChE inhibition and the resulting cholinergic over stimulation. Slight

histopathological changes were observed at high doses in the liver, adrenal glands and the kidneys. The observation from chronic and repeat dose studies included unstable heart rate and blood pressure, muscle cramps, skin flushing, diarrhoea, vomiting, increases in urinary frequency and epigastric cramping.

Delayed neurotoxicity is an important toxicological endpoint of a number of organophosphorus compounds. Kaplan *et al*. (1993) and Sherman (1995) reported delayed polyneuropathy in humans with signs evident weeks or months after the initial symptoms of chlorpyrifos exposure resolved. However, these findings were discounted by ATSDR (1997) because the studies lacked adequate exposure data and the cognitive complaints were non-specific, non-quantitative and possibly attributable to a wide variety of causes. The NRA (2000), on the other hand, considered that these indicated mild chlorpyrifos induced, reversible delayed polyneuropathy that is sometimes seen at very high exposure doses requiring aggressive antidotal therapy and artificial respiration. Thus these are unlikely to be seen after exposure to contaminated soil. Delayed neurotoxicity was not observed in chickens, the animal model usually used to determine this effect.

In a study by Zheng *et al*. (2000) it was reported that neonatal rats are more sensitive to cholinesterase inhibition effects in plasma and brain than juvenile and adult rats after a single oral dose of between 0.15 and 15 mg/kg. Unlike the US EPA, the NRA and NDPSC considered that the normal safety factors for interindividual variability used in combination with the No Observed Effects Level (NOEL) in humans for the most sensitive toxicological endpoint (plasma cholinesterase activity inhibition), are adequate for setting public health standards for repeated exposure of humans to low levels of chlorpyrifos.

### 5.2 REPRODUCTIVE, DEVELOPMENTAL, TERATOGENICITY, GENOTOXICITY AND CARCINOGENICITY

Chlorpyrifos did not cause major malformations or significant effects on most reproductive parameters in experimental animals (NRA, 2000). Sherman (1996) reported fetal defects of the brain, eyes, ears, palate, teeth, heart, feet, nipples, and genitalia. These findings were discounted in the recent NRA review (NRA, 2000) because the study did not adequately demonstrate an association with chlorpyrifos exposure.

Chlorpyrifos is not genotoxic (NRA, 2000).

There is insufficient information to assess the carcinogenic effects of chlorpyrifos in humans. Chlorpyrifos is not carcinogenic in animals.

## 6 CALCULATION OF GUIDELINE VALUES

The NRA review (NRA, 2000) identified the following oral administration studies as suitable for deriving an ADI for chlorpyrifos (Table 1).

**Table 1. Studies adequate for establishing an ADI for chlorpyrifos**

| Species | Duration | NOEL mg/kg/day | LOEL mg/kg/day | Adverse effect reported | Author |
|---|---|---|---|---|---|
| Mouse | 78 weeks | | 0.7 | Plasma ChE | Gur *et al*. (1991) |
| | | 0.7 | 6.1 | RBC ChE | |
| | | 0.7 | 6.1 | Brain ChE | |
| Mouse* | 2 years | 1.5# | | Carcinogenicity | Warner *et al*. (1980) |
| Rat | 2 years | 0.1 | 1.0 | Plasma ChE | Warner *et al*. (1980) |
| | | 0.1 | 1.0 | RBC ChE | |
| | | 1.0 | 3.0 | Brain ChE | |
| Rat | 2 years | 0.012 | 0.3 | Plasma ChE | McCollister *et al*. (1988) |
| | | 0.3 | 6 | Brain ChE | |
| Rat | 3 years | 0.1 | 1.0 | Plasma ChE | Crown *et al*. (1998) |
| | | 1.0 | 10 | RBC ChE | |
| | | 1.0 | 10 | Brain ChE | |
| Dog | 2 years | 0.01 | 0.03 | Plasma ChE | Salminen and Ma (1992) |
| | | 0.03 | 0.1 | RBC ChE | |
| | | 1.0 | 3.0 | Brain ChE | |
| Chicken | 1 year | < 2.5 | | Plasma ChE | Sherman and Herrick (1973) |
| Human | 9-28 days | 0.03 | 0.1 | Plasma ChE | Coulston *et al*. (1972) |
| | | 0.1 | - | RBC ChE | |

NRA (2000)
*Study suitable for oncogenicity determination only.
# Highest dose tested.

The critical study chosen by TGA for deriving the ADI was the human study by Coulston *et al*. (1972) in which the critical effect was plasma ChE inhibition with a NOEL of 0.03 mg/kg/day. An ADI of 0.003 mg/kg/day was established using a safety factor of 10 for intraspecies differences because of the adequacy of the human study.
An ADI for chlorpyrifos was set at 0-0.01 mg/kg/day in 1999 by the International Programme of Chemical Safety (IPCS) and JMPR.

The ATSDR has estimated Minimal Risk Levels (MRL), for acute (1-14 days), intermediate (>14-364 days) and chronic exposure (≥ 365 days) of 0.003, 0.003 and 0.001 mg/kg/day respectively. The MRL is similar to an ADI. The acute and intermediate MRLs are based on a NOEL of 0.03 mg/kg/day for plasma cholinesterase inhibition in human adult males (Coulston *et al*., 1972) and an uncertainty factor of 10 (intraspecies variability). The chronic MRL of 0.001 mg/kg/day is based on a NOEL of 0.1 mg/kg/day for cholinesterase inhibition in the two year study in rats by McCollister *et al*. (1974) and an uncertainty factor of 100 (10 for interspecies and 10 for intraspecies variability).

The US EPA oral RfD for chlorpyrifos is 0.003 mg/kg/day (IRIS, 1994). This guideline value is based on the Coulston (1972) study. No inhalation reference concentration has been set for this compound.

### 6.1 BACKGROUND EXPOSURE

As chlorpyrifos is one of the most widely used insecticides in Australia the number of people exposed is substantial as are the exposure routes (contaminated food, water, air

and soil). Indoor air, food and soil are the media with the highest degree of chlorpyrifos contamination, with lower contamination in ambient air, groundwater, and surface water (US EPA, 2000).

Exposure may occur in both occupational and non-occupational settings. Use for termite protection involves much higher rates of application than agricultural treatments.

### 6.2 FOOD

The 19th Australian Total Diet Survey (ANZFA, 2001), the most recent survey, reported that the estimated mean daily dietary exposures to detectable chlorpyrifos for adult males and females were 15.27 ng/kg/day and 15.96 ng/kg/day, respectively. Toddlers were estimated to be exposed to 230.27 ng/kg/day. Infants, girls and boys (12 years), were exposed to 107.04-157.85 ng/kg/day. The toddler, being the most sensitive receptor, is expected to have a mean daily dietary exposure to chlorpyrifos of 2.55% of the ADI (ANZFA, 2001). However, according to the NRA (NRA, 2000), the dietary intake from the 1992 survey was higher for all age groups and they used these estimates for their calculation of background exposure from food as shown in Table 2. Whilst the higher levels may have been due to agricultural practices at the time, the values provide an added degree of conservatism to estimates of dietary contribution to background exposure.

### 6.3 WATER

Chlorpyrifos is an occasional contaminant of surface waters.

### 6.4 AIR

According to a study of ambient air exposures to pesticides in Coffs Harbour (NSW) in the summer of 1992-1993 by Beard *et al*. (1995) chlorpyrifos was the most commonly detected pesticide. The maximum detected level was 208 ng/m$^3$ with a mean of 3.6 ng/m$^3$. These levels were consistent with applications of chlorpyrifos made to or around the home and did not correlate with the time of peak agricultural use.

The NHMRC Standing Committee on Toxicity (SCOT), in an assessment of the risk to public health from chlorpyrifos termiticide use in Australia, reported that levels in buildings did not exceed 1 µg/kg/day (NRA, 2000).

Mean indoor air concentrations following soil barrier treatments against termites were reassessed as part of an ERCP review. It was concluded that mean indoor air concentration did not exceed 1 µg/m$^3$ (NRA, 2000), i.e. a maximum of about 15% of ADI for a child (Table 2).

The NRA in their review tabulated estimated background daily intake of chlorpyrifos concentrations from dietary and residential exposures.

**Table 2 Estimated background daily intake of chlorpyrifos from various sources[1]**

| Population group* | Dietary exposure estimate µg/kg/day[1] (% ADI) | Residential Air exposure µg/kg/day[2] (% ADI) | Total exposure estimate µg/kg/day | Total Percentage of ADI %[3] |
|---|---|---|---|---|
| Adult | 0.49[4] (16.3) | 0.32 (10.6) | 0.81 | 27% |
| Children aged 12 years | 0.5[4] (16.7) | 0.44 (14.6) | 0.94 | 31% |
| Toddler aged 2 years | 0.63 (18.9) | 0.38 (12.6) | 1.01 | 34% |
| Infants aged 9 months | 0.52 (17.3) | 0.28 (9.3) | 0.80 | 27% |

NRA (2000)

*1 Based on groups used in the Australian Market Basket Surveys (AMBS).
Highest intake estimate (95th percentile) from AMBS 1992 in mg/kg/day

2 Based on a maximum exposure of 1 µg/m$^3$, and using air intake estimates from IPCS EHC 210 (1999).

3 Expressed as a percentage of the Acceptable Daily Intake (ADI) of 0.003 mg/kg/day

4 Females

## 7 SETTING A GUIDELINE VALUE

As children usually receive a higher exposure to soil contaminants per unit body weight than adults and as soil ingestion by small children is usually by far the most important exposure route, the HIL for chlorpyrifos will be based on the key target group of a two year old child.

### 7.1 DERIVATION OF HIL

The derivation of HIL is based on the following:

| | |
|---|---|
| Soil ingestion | 100 mg/ day |
| ADI | 0.003 mg/kg/day |
| Bioavailability from the soil | 100% |
| Weight of child | 13.2 kg |

### 7.2 BACKGROUND EXPOSURE

| | |
|---|---|
| Water | 10 % of ADI |
| Food | 20% of ADI |
| Residential exposure (air) | 12.7 % of ADI |
| Exposure from soil | 20% of ADI (default value) |

Given the uncertainties of determining background exposure form other sources and the widespread use of chlorpyrifos, the proportion of the ADI assigned to soil intake for standard setting should be set at 20%.

$$\text{Soil Concentration (mg/kg)} = \frac{\text{ADI} \times 0.2 \times 13.2 \times 10^6 \times 1}{100}$$

$$= 79.2$$

$$= 80 \text{ mg/kg}$$

Accordingly the recommended HIL for chlorpyrifos in soil is 80 mg/kg.

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