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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

July 23, 1999

SUBJECT: **Chlorpyrifos:** HED Preliminary Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Chemical No. 059101. Barcode: D257953.

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Attached is HED's preliminary risk assessment of the organophosphate pesticide, chlorpyrifos, for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. Cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity is not addressed in this document. The disciplinary science chapters and other supporting documents for the chlorpyrifos RED are also included as attachments as follows:

Report of the Hazard Identification Assessment Review Committee. Deborah Smegal (3/4/99; HED Doc No. 013249); Jess Rowland (12/7/98; HED Doc No. 013004)
Report of the FQPA Safety Factor Committee. Brenda Tarplee (4/5/99; HED Doc No. 013296)
Revised Product and Residue Chemistry Chapter. Steven Knizner (5/25/99; D256118)
Toxicology Chapter. Deborah Smegal (05/6/99; D255714)
Occupational/Residential Handler and Post-Application Residential Risk Assessment. D. Smegal/T. Leighton (6/30/99; D254880)
Agricultural and Occupational Exposure Assessment: Tim Leighton (7/22/99; D257954)
Acute Dietary Risk Assessment for Chlorpyrifos. (D. Soderberg 7/22/99, D257952)
Chronic Dietary Exposure Assessment for Chlorpyrifos. David Hrdy (6/1/99, D255452)

Anticipated Residues for Chronic Dietary Exposure Assessment for Chlorpyrifos RED. David Hrdy (6/1/99, D255452)
Chlorpyrifos Incident Review Update: Jerome Blondell (6/30/99).
Update of Incident Data on Chlorpyrifos for Domestic Animals. Virginia Dobozy (04/26/99; D255514)
Status of HED-Related Dow Agro Sciences Study Submissions that Impact the HED Preliminary Risk Assessment. D. Smegal (5/28/99)
Drinking Water Assessment from the Environmental Fate and Effects Division (EFED). Michael Barrett (11/13/99)
Chlorpyrifos. Possible Reduction of Residue Studies. S. Knizner to D. McNielly (4/7/1995; D212580)

HED's Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicological database for chlorpyrifos and selected toxicological endpoints for acute oral, chronic oral and for short-, intermediate and long-term dermal and inhalation exposure risk assessment on February 2, 1999, and February 22, 1999 (memorandum dated March 4, 1999). HED's FQPA Safety Factor Committee reviewed the hazard and exposure data for chlorpyrifos on November 8, 1998, February 22, 1999 and March 8, 1999 and recommended that the FQPA Safety Factor (as required by Food Quality Act of August 3, 1996) be reduced to 3X in assessing the risk posed by this chemical (memorandum dated April 5, 1999).

HED has attached a status summary of the Dow AgroSciences studies identified in the August 24, 1998 letter to Fred Hansen and Richard Rominger, and the HED-related studies identified in January 4, 1999 letter to Susan Wayland. In addition, the table contains a status summary of HED-related studies submitted in 1999, many of which have been evaluated and incorporated into the preliminary risk assessment.

In June 1997, the registrants of chlorpyrifos voluntarily agreed to measures designed to reduce household exposure to chlorpyrifos, as part of a Risk Reduction Plan. This voluntary plan involved deletion of indoor broadcast use, use as an additive to paint, direct application to pets (sprays, shampoos and dips), and indoor total-release foggers. The technical chlorpyrifos products have been amended to reflect the negotiated plan. The technical label limits end use product labeling to only those sites which are specified on its label. In addition, the registrants have implemented the following measures:

- revised labels for safer termiticide and pet care products per PR notice 96-7 on all termiticide labeling and 96-6 on all pet care product labeling and support the Agency efforts to expedite these changes for other products;
- accelerated education and training for pest control operators (PCOs) on these measures to reduce risk and exposure, label improvements, and implementation of recent PR Notices 96-7 (for termiticides) and 96-6 (for pet care products), and support the Agency efforts to expedite these changes for other products;
- undertaken epidemiological research and established a Blue Ribbon Panel to provide scientific direction for study design for chlorpyrifos; and
- continued the Poison Control Center Stewardship Project (University of Minnesota) for chlorpyrifos to monitor incident reporting related to chlorpyrifos. This includes follow-up on the identity of products and the circumstances responsible for exposure.

In addition, as part of this agreement, the registrants agreed to work with EPA to develop broad, market-wide policies for all indoor insecticides for a number of areas including:

- limiting household consumer use to only products packaged as ready-to-use;
- prohibiting use in inappropriate areas (e.g., toys, drapes, furniture);
- requiring PCOs to clean up spills and misapplications;
- requiring more training of PCOs and more supervision during application;
- reducing exposure by eliminating concentrates which require mixing;
- establishing specific protection measures for humans and pets during and immediately after application; and
- revising labels to include appropriate intervals between treatment (e.g., to replace "use as necessary", currently on some labels).

1.0 EXECUTIVE SUMMARY

The Health Effects Division (HED) has conducted a Preliminary Human Health Risk Assessment for the active ingredient chlorpyrifos for the purposes of making a reregistration eligibility decision (RED). The toxicological database is adequate to support reregistration. Residue chemistry requirements are substantially complete pending receipt of limited confirmatory data.

Chlorpyrifos, [O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl)-phosphorothioate], is a broad-spectrum, organophosphate insecticide that was first registered in 1965 to control foliage- and soil-borne insect pests on a variety of food and feed crops. It is one of the most widely used organophosphate insecticides in the U.S. and is one of the top five insecticides used in residential settings. There are approximately 850 registered products containing chlorpyrifos on the market. Registered uses include a wide variety of food crops (i.e., there are approximately 112 tolerances for food/feed commodities such as citrus, vegetable crops, tree fruits, etc.), turf and ornamental plants, greenhouses, sodfarms, as well as indoor products, structural pest control, and in pet collars. It is used in residential and commercial buildings, schools, daycare centers, hotels, restaurants and other food-handling establishments, hospitals, stores, warehouses, food manufacturing plants, vehicles, and livestock premises. In addition, it is used as a mosquitocide, and as an ear tag treatment of cattle. In 1998, the Dow AgroSciences estimated that 70% of the urban chlorpyrifos use involved termite control. Chlorpyrifos products are widely used by both homeowners and pest control operators (PCOs).

Chlorpyrifos, is formulated as a wettable powder, emulsifiable concentrates, dust, granular, bait, flowable concentrates, impregnated material, pelleted/tableted, pressurized liquids, and microencapsulated.

Because of its extensive use, the majority of the U.S. population is exposed to chlorpyrifos. Epidemiology data have reported measurable concentrations of the primary urinary metabolite, 3,5,6-trichloro-2-pyridinol (3,5,6-TCP) in 82% of 993 adults from the National Health and Nutrition Examination Survey III (NHANES III), while preliminary results from the recent Minnesota Children's Exposure Study found that 92% of the 89 children evaluated had measurable urinary concentrations of 3,5,6-TCP.

Hazard: Chlorpyrifos is moderately toxic following acute oral, dermal and inhalation exposures (toxicity category II). Chlorpyrifos is a reversible inhibitor of cholinesterase (ChE). Inhibition of ChE is the most sensitive toxicologic observation in all animal species evaluated and in humans, regardless of route or duration of exposure. In animals, significant inhibition of plasma and red blood cell (RBC) ChE occur at doses below those that cause brain ChE inhibition. Data from two human studies suggest that humans may be more sensitive to plasma ChE inhibition than animals following acute and short-term oral exposure and acute dermal exposure. Chlorpyrifos did not induce treatment-related tumors or carcinogenicity in two chronic rat or two chronic mouse studies. Developmental and reproductive effects have been observed in rats, rabbits and/or mice, but only at doses that induced maternal or parental toxicity. Studies in the scientific literature suggest that neonates may be more sensitive to oral chlorpyrifos exposure than adults for ChE inhibition and behavioral effects (Moser and Padilla 1998, Moser et al. 1998, Zheng et al. 1999). This increased sensitivity has been attributed to a reduced capacity to detoxify

chlorpyrifos. Other studies in the literature indicate that chlorpyrifos affects the developing brain of neonates (Whitney et al. 1995, Campbell et al. 1995, Song et al. 1997, Slokin 1999, Johnson et al. 1998). For this purposes of this assessment, HED has concluded that the primary metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (3,5,6-TCP), is not of toxicologic concern because 3,5,6-TCP does not induce cholinesterase inhibition.

The toxicity endpoints used in this document to assess hazards include acute dietary and chronic dietary reference doses (RfDs), and short-, intermediate- and long-term dermal and inhalation doses. In light of the developing Agency policy on use of toxicology studies employing human subjects, HED selected doses and endpoints for risk assessment based solely on animal studies. Therefore, this document contains risk assessments based on animal toxicity studies.

The acute dietary RfD of 0.005 mg/kg/day is based on a no-observed adverse effect level (NOAEL) of 0.5 mg/kg/day from an acute oral rat blood time-course study that observed 28-40% plasma cholinesterase (ChE) inhibition 3-6 hours after dosing male rats with a single dose of 1 mg/kg/day (the lowest-observable adverse effect level, LOAEL). The chronic RfD of 0.0003 mg/kg/day is based on an oral NOAEL of 0.03 mg/kg/day from a 2-year dog study that observed significant plasma and red blood cell (RBC) ChE inhibition in both sexes at a dose level of 0.1 mg/kg/day (LOAEL). An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain the RfDs.

A route-specific short-term dermal NOAEL of 5 mg/kg/day from a 21-day dermal rat study has been identified based on plasma and RBC ChE inhibition of 45% and 16%, respectively at 10 mg/kg/day (LOAEL). Therefore, a dermal absorption adjustment is not necessary. The intermediate- and long-term dermal NOAELs and long-term inhalation NOAEL are 0.03 mg/kg/day based on significant plasma and RBC ChE inhibition that occurred at 0.1 mg/kg/day in a 2-year oral dog study. Because an oral NOAEL was selected, a 3 percent dermal absorption factor, and a 100% default inhalation absorption factor (i.e., inhalation and oral absorption are equivalent) were used. Dermal absorption was estimated to be 3 percent based on the ratio of the oral LOAEL of 0.3 mg/kg/day from the rat developmental neurotoxicity study to the dermal LOAEL of 10 mg/kg/day from the 21-day rat dermal study. This absorption factor is comparable to the dermal absorption estimated from human data of 1-3%.

The short- and intermediate-term inhalation NOAEL is 0.1 mg/kg/day from two separate 90-day rat inhalation studies that did not observe effects at the highest vapor concentration tested. At higher oral doses of 0.3 mg/kg/day (LOAEL) 43% plasma and 41% RBC ChE inhibition relative to controls were observed in rats.

FQPA Safety Factor: The Food Quality Protection Act (FQPA) Safety Factor Committee determined that the FQPA safety factor should be reduced from 10X to 3X. The factor is to be applied to acute and chronic dietary and residential exposures. The factor was **reduced to 3X** due to the apparent absence of increased susceptibility in the guideline reproductive and developmental studies and no quantitative evidence of increased susceptibility in the developmental neurotoxicity study. However, the Committee had remaining concerns about the qualitative evidence of increased susceptibility in the developmental neurotoxicity study at the high dose, and reports of increased susceptibility of young rats compared to adults reported in the

scientific literature that can not be discounted as well as widespread use of chlorpyrifos and the potential for exposure to infants and children.

Dietary Exposure: HED conducted the most highly refined Tier 3/4 and Tier 4 acute probabilistic and chronic deterministic dietary (food) exposure analyses possible using the Dietary Exposure Evaluation Model (DEEM). Both the acute and chronic dietary analyses incorporate monitoring data obtained from U.S. Department of Agriculture's (USDA's) Pesticide Data Program (PDP), the Food and Drug Administration's (FDA's) Surveillance Monitoring Program, in addition to monitoring data from Dow AgroSciences' 1993 National Food Survey (NFS), and very limited field trial data. Percent crop treated data were also used to refine the exposure estimates. The Tier 3/4 analyses used data for only two commodities (ground beef and pork) from the NSF, whereas the Tier 4 analyses used data for all nine commodities from the NFS. The primary difference between the Tier 3/4 and Tier 4 risk results is the residue data used for apples. The NFS data supplied by Dow for the Tier 4 risk assessment are now somewhat dated (samples were collected in 1993) in comparison to more recent PDP and FDA data, and are limited (200 samples). For some commodities included in the NFS, more recent and extensive data are available from monitoring programs. For example, the NFS included 200 apple samples, but PDP collected 1908 samples from 1994-1997 and FDA collected 1342 samples from 1992-1997. Because of the limited and dated NFS data, the Agency elected to conduct a Tier 3/4 analysis, which only incorporated NFS data for beef and pork, because those are the best data available for meat. The Agency believes that the Tier 3/4 exposure and risk estimate most accurately reflects current dietary exposures.

In both assessments, exposure (consumption) was compared to a reference dose (RfD) reflecting retention of the FQPA 3x factor (e.g. a population adjusted dose, PAD). HED considers dietary residue contributions greater than 100% of the PAD to be of concern. The acute and chronic PADs are 0.0017 and 0.0001 mg/kg/day, respectively. The Tier 3/4 and Tier 4 acute and the Tier 3/4 chronic dietary exposures (without the food handling establishment use), exceed HED's level of concern. **Acute dietary** exposure at the 99.9th percentile based on a highly refined probabilistic analysis comprised 44-56% of the aPAD for the general population and 120-160% of the aPAD for the most highly exposed subgroup, children (1-6 years). All of the Tier 4 **Chronic dietary** exposure, without consideration of food handling establishment use, are below HED's level of concern, however the Tier 3/4 exposure comprised 48% of the cPAD for the general population and 107% of the cPAD for the most highly exposed subgroup, non-nursing infants (<1 years). Tier 3/4 and Tier 4 chronic dietary exposure, with the food handling establishment use comprised 210-278% of the cPAD for the general population and 790-952% of the cPAD for the most highly exposed subgroup, non-nursing infants.

Water Exposure: The available environmental fate data suggest that chlorpyrifos has a low potential to leach to groundwater in measurable quantities from most typical agricultural uses, except following termiticide use. Although limited, the available data indicate that the primary metabolite of chlorpyrifos, 3,5,6-TCP is more mobile, and significantly more persistent in many soils, especially under anaerobic conditions. However, the Agency has concluded that 3,5,6-TCP is not of toxicologic concern. The Environmental Fate and Effects Division (EFED; memo by Michael Barrett dated November, 13, 1998) has provided a screening-level drinking water assessment using simulation models and an analysis of available monitoring data to estimate the

potential concentrations of chlorpyrifos in ground and surface water.

EFED conducted an analysis of over 3000 groundwater monitoring data available in U.S. Geological Survey's National Water Quality Assessment (NAWQA) Program databases, and in EFED's Pesticides in Ground Water Data Base (PGWDB), and evaluated 20 NAWQA study units for surface water. Chlorpyrifos was infrequently detected in groundwater (< 1% of the 3000 wells), with the majority of concentrations reported to be <0.01 μg/L, with a maximum detected concentration of 0.65 μg/L in the PGWDB. Groundwater concentrations following termiticide use are much higher, with a maximum reported concentration of 2000 μg/L. In surface water, chlorpyrifos was detected at frequencies up to 26% of 604 samples from the 20 NAWQA study sites in 1997 and in 65% of 57 samples from Georgia, Alabama and Florida in 1994. The maximum reported dissolved chlorpyrifos concentration in surface water is 0.4 μg/L, with the majority of chronic concentrations < 0.1 μg/L. However, EFED notes that the monitoring data are not available for the most vulnerable watersheds or groundwater where chlorpyrifos use is pervasive.

EFED also performed screening-level model estimates of chlorpyrifos concentrations in groundwater using SCI-GROW and in surface water using Tier I GENEEC or Tier II PRZM/EXAMS. Inputs to the models included high exposure agricultural scenarios for major crops (alfalfa, corn, citrus, and tobacco) at the maximum application rates. The estimated concentration of chlorpyrifos in groundwater using the SCI-GROW screening model is 0.11 μg/L (for sweet corn use). Estimated average and peak concentrations of chlorpyrifos in surface water using the PRZM/EXAMS screening model are 6.7 μg/L and 31 μg/L, respectively.

Based on model estimates and monitoring data, EFED has provided HED with estimates of chlorpyrifos concentrations in drinking water of **0.4 μg/L for acute and chronic surface water** (based on monitoring data) and **0.1 μg/L for acute and chronic groundwater** (based on modeling), except for **termiticide use** areas, where EFED reports a concentration of **2000 μg/L (based on monitoring) for acute and chronic groundwater risk assessments.** HED did not calculate Drinking Water Levels of Comparison (DWLOCs) for chlorpyrifos because the acute and chronic dietary risks, as well as short-, intermediate- and long-term residential postapplication risks alone exceed HED's level of concern. Therefore, in effect the DWLOCs would be zero.

Acute exposure to the EFED-recommended drinking water estimates for ground and surface water, except termiticide use, represent less than 3% of the aPAD, while chronic exposures represent up to 40% of the cPAD for children (the most highly exposed population). Exposures to the chlorpyrifos groundwater concentrations resulting from termiticide use for either acute or chronic durations result in exposures that exceed 100% of the aPAD and cPAD, and therefore, exceed HED's level of concern.

Occupational and Residential Exposure: Occupational and residential exposures to chlorpyrifos can occur during handling, mixing, loading and application activities. Occupational postapplication exposure can occur for agricultural workers during scouting, irrigation and harvesting activities. Residential postapplication exposure can occur following treatment of lawns, or residences for cockroaches, carpenter ants, termites, and other insects. In addition,

there is a potential for inadvertent oral exposure to children from eating chlorpyrifos-treated turf and soil. Postapplication exposure to children can occur in locations other than the home, including schools, daycare centers, playgrounds, and parks. There is insufficient use information and exposure data to assess exposure resulting from use in vehicles (i.e., planes, trains, automobiles, buses, boats) and other current label uses such as treatment of indoor exposed wood surfaces, supermarkets, theaters, furniture, and draperies, etc. However, HED has concern for these uses based on the scenarios assessed within this document.

Based on toxicological criteria and potential for exposure, HED has conducted dermal and inhalation exposure assessments for: occupational and residential handlers; occupational postapplication; and residential postapplication dermal, and inhalation exposure to adults and children as well as inadvertent oral exposure to children. The duration of exposure is expected to be short-, and intermediate-term and in some instances long-term for the occupational handler and postapplication residential exposure, intermediate for occupational postapplication, and short-term for the residential handler. The exposure duration for short-term assessments is 1 to 7 days. Intermediate-term durations are 1 week to several months, and long-term exposures are durations greater than several months. For dermal and inhalation risk assessment, risk estimates are expressed in terms of the Margin of Exposure (MOE), which is the ratio of the NOAEL selected for the risk assessment to the exposure. For occupationally exposed workers, MOEs >100 (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability) do not exceed HED's level of concern. For residential populations, MOEs > 300, which includes an additional 3x FQPA safety factor, do not exceed HED's level of concern.

Occupational risk estimates exceed HED's level of concern. The **results of the intermediate-term agricultural handler** assessments indicate that none of the potential exposure scenarios provide total dermal and inhalation MOEs greater than or equal to 100 at **baseline** attire (i.e., long pants, long sleeved shirts, no gloves) and only three of the 16 at the **maximum personal protective equipment (PPE)** of coveralls over long pants, long sleeved shirts, and chemical resistant gloves while using open systems. Using **engineering controls** (i.e., closed systems), only 5 of the 16 scenarios evaluated have total MOEs greater than or equal to 100. Even within these acceptable scenarios, not all of the application rates/crops have MOEs greater than or equal to 100. There are insufficient information and data to assess the seed treatment uses, dip applications (e.g., preplant peaches), and dry bulk fertilizer applications to citrus orchard floors. These scenarios are of concern given the results from the other scenarios assessed. The agricultural handler assessments are believed to be reasonable high end representations of chlorpyrifos uses. Eleven of the scenarios were evaluated based on data obtained from five chemical-specific studies submitted by Dow AgroSciences.

The results of the PCO handler assessment in residential settings for intermediate and/or long-term exposure scenarios indicate that most of the MOEs are less than 100, and therefore exceed HED's level of concern. The only intermediate-term scenarios that result in a MOE consistently above 100 is the use of a 0.5% ready-to-use formulated product (MOE = 140), and lawn care professionals that wear PPE and mix and load lawn products for intermediate durations (i.e., less than several months a year) (total dermal and inhalation MOEs 140-160). The majority of risks were estimated based on chemical-specific biomonitoring studies submitted by Dow

AgroSciences (i.e., indoor crack and crevice treatment, broadcast turf application, ready-to-use formulated product, and pre- and post-construction termiticide treatment) in which the PCOs wore label-specified personal protective equipment (PPE). Several of these studies did not apply the product at the maximum label rate, or only evaluated exposures for a few hours (i.e. 1-3 hours) of the work day, and consequently could underestimate exposures and risks to PCOs. Overall, the exposures and risks for PCOs based on the chemical-specific biomonitoring studies are considered to be central tendency estimates because they evaluated less than a full day's exposure at the maximum label rate or they exclude accidental exposure (e.g., exposure resulting from a broken hose). In the absence of chemical-specific data, PCO exposures were estimated using data from Pesticide Handlers Exposure Database (PHED) or the Draft Residential SOPs. The PHED data used for the mixer/loader for lawn treatment, and granular bait application (hand, belly grinder and push-type spreader) scenarios are representative of the chlorpyrifos uses as the surrogate data were monitored for the same uses. In the absence of surrogate data, (e.g., dust application) the Draft Residential SOP assumptions were used.

The results of the **intermediate-term postapplication** assessments for **workers at agricultural use sites** indicate that restricted entry intervals (REIs) need to be established. The potential for dermal contact during postapplication activities (e.g., harvesting) is assessed using a matrix of potential dermal contact rates by activity and associated crops with groupings of "low", "medium", and "high". The REIs range from 12 days for the "low" crop grouping to 20 days for the "high" crop grouping. REIs for citrus and tree nut and fruit crops are 5 to 6 days for harvesting. A postapplication entry restriction for scouts in citrus and tree nut and fruit crops is 4 days. The timing of the applications are important to note because most of the applications to trees (except apples) are to the bark during the dormant to early season. Furthermore, long pre-harvest intervals (PHIs) exist for crops such as citrus. Even though there are insufficient information (e.g., timing of applications–dormant/bark versus foliar treatments) and data to assess postapplication activities for ornamental, sodfarm, and soil incorporated uses, these uses are believed to require long REIs (e.g., high application rates and high potential for dermal contact). The occupational postapplication assessment is believed to be reasonable high end representations of chlorpyrifos uses. Three of the four registrant-submitted Dislodgable Foliar Residue (DFR) studies, in addition to two registrant assessments of their DFR data are included in this assessment.

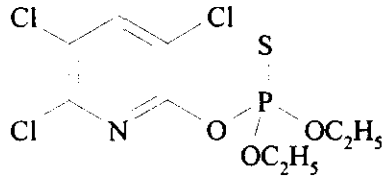
Residential risk estimates exceed HED's level of concern. Eight of the nine **short-term residential handler** exposure scenarios evaluated have total dermal and inhalation MOEs (based on typical or maximum usage rates) that exceed HED's level of concern defined by a target MOE of 300. MOEs for the residential handler ranged from 1 to 897 for **dermal** risk, from 2.5 to 56,700 for **inhalation** risk, and from 0.8 to 880 for **total** dermal and inhalation risk. Application of a 0.5% active ingredient ready-to-use formulation by a resident was the only scenario that resulted in total MOEs greater than 300. In some instances, when the product is not applied at the maximum label rate, is maximally diluted and/or is applied using different equipment, the MOEs are above 300. These additional analyses were conducted to assist in risk mitigation and management decisions. Only one of the residential handler scenarios was evaluated using chemical-specific data submitted by Dow AgroSciences.

The results of the **residential postapplication** exposure scenarios indicate that seven of the eight scenarios evaluated have MOEs that are less than 300, and therefore exceed HED's level of concern. An additional scenario could not be quantitatively evaluated (insecticidal dust product use) due to an absence of chemical-specific data and recommended procedures in the residential SOPs. MOEs ranged from 7.5 to 3700 for **total** dermal, inhalation and oral (in the case of children) risk. The only scenario that resulted in a MOE consistently above 300 is the aerial and ground-based fogger mosquitocide application. The MOEs following termiticide treatment of crawlspace homes were above 300, however, treatment of other construction type homes for termites resulted in MOEs below 300 for children. The majority of residential postapplication risks were estimated based on chemical-specific studies submitted by Dow AgroSciences (i.e., crack and crevice treatment of the kitchen and bathroom, broadcast treatment of turf with chlorpyrifos spray and granules, and termiticide treatment). The exposure and risk estimates based on the chemical-specific studies are considered to be reasonable central-tendency estimates (i.e., arithmetic mean exposure was used to calculate risk). Because these studies were conducted in adults, conservative assumptions were used to estimate child exposures.

An **aggregate risk** estimate was not conducted for any duration (i.e., acute, chronic, short- or intermediate-term) because the some of the acute and chronic dietary exposures, and the total residential MOEs (dermal, inhalation, and inadvertent oral exposures) for all the residential post-application exposure scenarios, except mosquitocide use, alone exceed HED's level of concern.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Technical chlorpyrifos is a white crystalline solid with a melting point of 41.5-43.5° C. Chlorpyrifos is stable in neutral and acidic aqueous solutions; however, stability decreases with increasing pH. Chlorpyrifos is practically insoluble in water, but is soluble in most organic solvents (i.e., acetone, xylene and methylene chloride). Chlorpyrifos is not particularly volatile based on its low vapor pressure of 1.87×10^{-5} mmHg at 20°C (Merck Index, 11th Edition). Its maximum attainable vapor concentration is 25 ppb at 25° C.



Empirical Formula:	$C_9H_{11}Cl_3NO_3PS$
Molecular Weight:	350.6
CAS Registry No.:	2921-88-2
Shaughnessy No.:	059101

The persistence of chlorpyrifos in soil varies depending on soil type, and environmental conditions. The typical aerobic soil metabolism half life ($T_{½}$) ranges from 11 to 180 days, with a mean of 63 days. Much longer soil half lives of 175 to 1576 days have been reported for termiticide application rates (Memorandum from M. Barrett to S. Knizner, Drinking Water Assessment of Chlorpyrifos, November 13, 1998). The soil/water partition coefficient (K_{oc})

value ranges from 360 to 31000, indicating that it is not very mobile in soils.

Technical Grade Active Ingredient (TGAI) data requirements concerning the DowElanco 99% T (EPA Reg. No. 62719-44) and the 97% T (EPA Reg. No. 62719-15) are satisfied. Guideline 830.6314 data requirements remain outstanding for the DowElanco 99% T. There are 45 chlorpyrifos Manufacturing-Use Products (MPs). Data remain outstanding for many MPs. Product chemistry data requirements will be complete, provided that the registrants submit the data required as identified in the Revised Product and Residue Chemistry Chapter (Memorandum from S. Knizer to M. Hartman, May 25 1999, D256118) for the chlorpyrifos MPs. In addition, the registrants must either certify that the suppliers of starting materials and the manufacturing processes for the chlorpyrifos technicals and manufacturing-use products have not changed since the last comprehensive product chemistry review or submit complete updated product chemistry data packages.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

The toxicology database is complete and adequate to assess the health hazards resulting from exposure to chlorpyrifos. Chlorpyrifos is an organophosphate compound that is a reversible inhibitor of cholinesterase (ChE). Inhibition of ChE is the most sensitive toxicologic observation in all animal species evaluated and in humans, regardless of exposure duration. In animals, significant inhibition of plasma and red blood cell (RBC) ChE occur at doses below those that cause brain ChE inhibition. In animals, significant plasma and RBC ChE have been observed at oral doses as low as 0.025 to 1 mg/kg/day following exposure for 10 days to two years, while significant brain ChE inhibition has been observed at oral doses as low as 1 to 5 mg/kg/day following exposure for 90 days to two years. Data from two human studies suggest that humans may be more sensitive to plasma ChE inhibition than animals following acute and short-term oral exposure and acute dermal exposure.

HED has concluded that the primary metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (3,5,6-TCP), is not of toxicologic concern because 3,5,6-TCP does not induce cholinesterase inhibition.

Rats acutely exposed to chlorpyrifos exhibited peak plasma ChE inhibition of 28-40% 3-6 hours after exposure at 1 mg/kg, while plasma, RBC and heart ChE inhibition of 45%, 17% and 19%, respectively were observed in rats 24 hours following a single dose of 5 mg/kg. The acute oral NOAEL for plasma ChE inhibition is 0.5 mg/kg/day. Clinical signs of neurotoxicity, in the absence of neuropathology, were observed in rats exposed to a single oral dose of 50 mg/kg as evidence by decreased motor activity, and increased incidence of clinical signs consistent with organophosphate intoxication. Chlorpyrifos was negative in the delayed neurotoxicity study in hens at single doses of 50, 100 or 110 mg/kg. However, acute oral exposure to hens at 150 mg/kg/day caused >80% inhibition of neurotoxic esterase (NTE) 4 days after exposure (Capodicasa et al. 1991). In rats, chlorpyrifos failed to inhibit NTE at single doses up to 100 mg/kg. There is evidence that NTE inhibition is related to organophosphate-induced delayed neuropathy (OPIDN).

Following longer-term exposures, there was no evidence of neurotoxicity or neuropathology in rats exposed at doses up to 15 mg/kg/day for 13 weeks. However, in the developmental neurotoxicity study, pregnant dams exposed to 0.3 mg/kg/day for approximately 27 days exhibited 43% and 41% inhibition of plasma and RBC ChE activity, while dams exposed to 5 mg/kg/day exhibited clinical signs of neurotoxicity, including fasciculations (muscle twitching), hyperpnea (increased respiration), and hyperactivity. Cholinesterase inhibition (68% plasma, 56% RBC and 8% brain) was also noted in rats exposed to 1 mg/kg/day chlorpyrifos for 4 weeks in the cognitive study, while clinical signs of toxicity were not observed until higher doses of 3 mg/kg/day for miosis (pupil contraction) and 10 mg/kg/day for salivation and tremors.

Several subchronic studies are available for chlorpyrifos including two oral rat studies, one oral dog study, a 21 day dermal toxicity study in rats, and two inhalation studies in rats. The most sensitive toxicological endpoint following subchronic oral exposure is inhibition of plasma and RBC ChE in dogs at 0.22 mg/kg/day and plasma inhibition in rats at doses as low as 0.025 mg/kg/day. Rats exposed to higher doses also exhibited increased brain and heart weight, adrenal gland effects and decreased body weight gain at 1 mg/kg/day and hematological alterations suggestive of anemia at higher doses of 10 mg/kg/day. No adverse effects were noted in rats exposed via inhalation to the highest attainable vapor concentration of 20.6 ppb (287 $\mu g/m^3$). No adverse effects were observed in the 21-day dermal study in rats at doses as high as 5 mg/kg/day. However, in a 4-day dermal probe study, rats dermally exposed to doses of 0, 1, 10, 100, or 500 mg/kg/day exhibited reductions in plasma and RBC ChE activities at doses of 10 to 500 mg/kg/day. The 21-day dermal NOAEL is 5 mg/kg/day based on a 45% and 16% inhibition of plasma and red blood cell cholinesterase, respectively in rats dermally exposed to 10 mg/kg/day for 4 days.

Chlorpyrifos was evaluated for carcinogenic potential in both rats (2 studies), and mice (2 studies). There was no evidence of carcinogenicity. Chlorpyrifos is not mutagenic in bacteria, or mammalian cells, but did cause slight genetic alterations in yeast and DNA damage to bacteria. In addition, chlorpyrifos did not induce chromosome aberrations in vitro, was not clastogenic in the mouse micronucleus test in vivo, and failed to induce unscheduled DNA synthesis in isolated rat hepatocytes.

Chlorpyrifos was evaluated for chronic toxicity in rats, mice and dogs. In all animal species, the most sensitive toxicological endpoint is inhibition of plasma, RBC and brain ChE that occurred at levels in the range of 0.03 to 1 mg/kg/day. Dogs appear to be the most sensitive species for cholinesterase inhibition and systemic effects, as noted by increased liver weights in dogs exposed to 3 mg/kg/day. Rats exposed to 7-10 mg/kg/day had decreased body weight and decreased body weight gain, ocular effects, adrenal gland effects and altered clinical chemistry and hematological parameters. Mice appear to be the least sensitive, as exposure to 45-48 mg/kg/day resulted in decreased body weight and an increased incidence of non-neoplastic lesions (i.e., keratitis, hepatocyte fatty vacuolation).

Chlorpyrifos was evaluated for developmental toxicity in rats, mice and rabbits. In one rat study, developmental effects (increased post-implantation loss) were noted at 15 mg/kg/day (HDT), that were also associated with maternal toxicity, while another rat study failed to observe

developmental effects at 15 mg/kg/day. Developmental effects were also noted at higher doses in mice at 25 mg/kg/day (minor skeletal variations, delayed ossification and reduced fetal weight and length) and rabbits at 140 mg/kg/day (decreased fetal weights and crown rump lengths, and unossified xiphisternum and/or 5th sternebra). However, in both mice and rabbits, the developmental effects occurred at maternally toxic doses as indicated by reduced weight gain, and food consumption in both species, and increased mortality in mouse dams. In the developmental neurotoxicity study in rats, the pups of the 5 mg/kg/day group exhibited decreased body weight/body weight gain and food consumption in both sexes, reductions in pup viability, delays in development, decreased brain weight and morphometric alterations in the brain. However, these effects were observed in the presence of maternal toxicity as evidenced by fasciculations, hyperpnea and hyperactivity.

Chlorpyrifos induced reproductive toxicity in rats, but only at dose levels that induced parental toxicity. Reproductive effects included reduced pup weights and increased pup mortality, while parental effects included inhibition of plasma, RBC and brain cholinesterase activities as well as histological lesions of the adrenal gland (vacuolation of cells of the zona fasciculata).

HED has reviewed two human studies conducted with chlorpyrifos submitted by the registrant (MRID 95175, Accession No. 249203). A third human study that evaluated a single dose exposure was recently submitted on April 27, 1999 and is currently being reviewed by the Agency. In the first study (MRID No. 95175; Coulston et al., 1972), male volunteers from Clinton Correctional Facility (4/dose group) were given daily oral (tablet) doses of 0, 0.014, 0.03, or 0.1 mg/kg chlorpyrifos technical for 7 weeks, 9 days, 21 days and 28 days, respectively. Significant 36-82% plasma ChE inhibition relative to baseline was observed after 9 days of treatment with 0.1 mg/kg/day chlorpyrifos. In addition, one of the four men in the 0.1 mg/kg/day developed possible cholinergic clinical signs on day 8 (blurred vision, runny nose and a feeling of faintness). Exposure was discontinued on day 9 in this dose group due to plasma cholinesterase inhibition that exceeded the study investigator's guideline of 20%-30%. No significant plasma ChE inhibition was observed in the men exposed to 0.03 mg/kg/day for 21 days or at any other dose that could be attributed to treatment. No effects on RBC ChE were found at any dose that could be attributed to treatment. A gradual recovery was observed in plasma ChE values equaling baseline values by day 25 of the recovery period. It should be noted that the registrant contends that the clinical signs were attributed to a cold, and not chlorpyrifos exposure. HED believes that blurred vision is a typical cholinergic sign of ChE inhibition, and can not be attributed to a common cold (February 2, 1998 HIARC Report, HED Doc No. 012471).

An acute oral and dermal pharmacokinetic study (Nolan et al. 1982, Accession No. 249203) dosed six men once with 0.5 mg/kg orally and four weeks later dosed five of these same men with 5 mg/kg dermally, and one man with 0.5 mg/kg dermally. No signs or symptoms were observed in any of the subjects, but unlike the previous study, the primary focus of this study was pharmacokinetics. Men orally exposed to 0.5 mg/kg chlorpyrifos exhibited peak plasma ChE inhibition of 64-85%, 12 to 24 hours post-exposure and peak RBC ChE inhibition of 11-52% on post-exposure day 4. Men dermally exposed to 5 mg/kg chlorpyrifos exhibited peak plasma ChE inhibition of 27-45% on day 3, and mean RBC ChE inhibition of 8.6% on day 4. The return of

plasma ChE activity to pre-dose levels required about 30 days. On the basis of urinary excretion of the 3,5,6-trichloro-2-pyridinol (3,5,6-TCP) metabolite, the minimum oral absorption of chlorpyrifos was estimated at 70% and the minimal dermal absorption at 1-3%. Because the proportion of the administered dose metabolized to this pyridinol is unknown, these estimates are considered minimum values (i.e., absorption could be higher). The mean pharmacokinetic half-life for 3,5,6-TCP in the urine was approximately 27 hours following both oral and dermal exposure.

As noted previously, data from the two human studies suggest that humans are more sensitive to plasma ChE inhibition than animals. For example, in animals, the acute oral (single dose) NOAEL is 0.5 mg/kg/day, while humans exposed to a single oral 0.5 mg/kg/day dose exhibited 64-85% plasma ChE. Based on an overall assessment of the plasma and RBC ChE inhibition data, the HIARC identified an animal NOAEL and LOAEL of 0.03 mg/kg/day and 0.1 mg/kg/day, respectively for longer term exposures (>90 days), while humans exposed to 0.1 mg/kg/day for only 9 days exhibited 36-82% plasma ChE inhibition and possible clinical signs (blurred vision). The short-term dermal NOAEL in animals is 5 mg/kg/day based on plasma and RBC ChE inhibition observed at 10 mg/kg/day, while humans exposed dermally for one day to 5 mg/kg/day exhibited 27-45% plasma ChE inhibition.

In the rat, chlorpyrifos is excreted primarily in the urine (84%) with lesser amounts excreted in the feces (5%) within 72 hours. The metabolism of chlorpyrifos was extensive, and no unchanged parent compound was found in the urine. The major urinary metabolites were 3,5,6-TCP, as well as glucuronide and sulfate conjugates of TCP.

Scientific Literature

A number of studies published in the scientific literature have also been considered by the Agency and are discussed in the Hazard Identification and Assessment Review Committee (HIARC) February 2, 1998 report (HED No. 012471) and December 7, 1998 report (HED No. 013004). Summaries of most of these studies, as presented in the HIARC report, are presented in the attached Toxicology Chapter memorandum from D. Smegal to M. Hartman, May 6, 1999, D255714, and in the attached December 7, 1998 HIARC Report (HED No. 013004). The HIARC concluded that there is sufficient evidence in the scientific literature to conclude that exposure to chlorpyrifos results in increased susceptibility to neonates as compared to adult rats.

The Committee reviewed oral studies in animals that investigated the issues of differential sensitivities between adults and young animals following *in utero* and/or postnatal exposure to chlorpyrifos. In one of the studies, Moser and Padilla (1998) compared the effects of acute oral chlorpyrifos exposure in adult (70 days of age) and young (postnatal day 17) rats and observed that neonatal rats (10-27 days of age) were between 5-7 times more sensitive than adults to acute doses of chlorpyrifos at 75-100% of the maximum tolerated dose, with greater sensitivity identified in the youngest neonates. In this study, doses were administered by gavage at levels that were selected to produce similar effects in young and adult rats; adults received 80 mg/kg and pups received 15 mg/kg. The study authors concluded that: 1) young rats show similar behavioral changes (functional observation battery and motor activity), although at a 5-fold

lower dose; 2) the onset of maximal effects is somewhat delayed in the young rats, 3) ChE activity tends to recover more quickly in young rats, but; 4) the young rats appear to have more extensive muscarinic receptor down-regulation; and 5) young rats show no gender-related differences.

In a more recent publication, age-related sensitivity was reported based on a comparison of young (post-natal day 17), adolescent (post-natal day 27) and adult rats given a single oral dose of 20 mg/kg (Moser et al. 1998). In this study, there was generally less brain ChE inhibition and fewer behavioral effects with increasing age. The authors suggest that differences in detoxifying enzymes correlate with the age-related differences in behavioral and biochemical effects, and may play a role in the differential sensitivity to chlorpyrifos.

Another study presented at the 1999 Society of Toxicology Meeting demonstrated that 7-day old neonates administered single oral doses of 0.45 to 1.5 mg/kg chlorpyrifos were more sensitive than adults to plasma and diaphragm cholinesterase inhibition (Zheng et al. 1999).

Neonatal rats were shown to be much more sensitive to acute doses of chlorpyrifos at levels near the maximum tolerated dose than are adult rats, as measured by lethality (LD10 values) following subcutaneous injection (Pope et al. 1991). In another study, neonatal rats were about two times more sensitive than adult rats to 50% acetylcholinesterase (AChE) inhibition following subcutaneous injection (Pope and Liu 1997). While, HIARC acknowledges that the subcutaneous exposure is not a route which is anticipated for human exposure, the results of these studies contribute to the weight-of-the-evidence in assessing age-related differences in susceptibility to chlorpyrifos.

Other literature studies demonstrated that young rats have less capacity to detoxify chlorpyrifos and suggest that a lack of detoxifying enzymes in young rats could at least partially explain the increased sensitivity to chlorpyrifos. Detoxification enzymes that were shown to have lower activity in young rats compared to adults include carboxylesterase (CaE; which can bind to OPs and reduce the effective concentration at the target enzyme site), A-esterase (which can hydrolyze OPs to form nontoxic metabolites) (Chanda *et al.*) and chlorpyrifos-oxonase (CPFOase) (Mortensen *et al.*).

In addition, several studies in the literature indicate that chlorpyrifos affects the developing brain of neonates during cell division (Whitney et al. 1995, Campbell et al. 1997, Song et al. 1997, Slokin 1999, Johnson et al. 1998)

3.2 Acute Toxicity

Chlorpyrifos is moderately toxic following acute exposures. The oral LD_{50} values for technical chlorpyrifos are higher in rats (163 and 137 mg/kg for males and females, respectively) than mice (62.5 mg/kg, toxicity category II) or chicks (32 mg/kg, toxicity category 1). Guinea pigs and rabbits are less sensitive to acute toxicity than rats as noted by the oral LD_{50} values of 504 mg/kg and 1000-2000 mg/kg, respectively (both category II). Chlorpyrifos was not acutely neurotoxic when given to hens at a single oral dose of 50 mg/kg (the LD_{50}), 100 or 110 mg/kg.

In rats, the LC_{50} was greater than 0.2 mg/L (or 200 mg/m^3), which is normally assigned toxicity category II. This study is classified as Supplementary because only nominal concentrations were measured. Acute toxicity values and categories for the technical grade of chlorpyrifos are summarized in the following table.

Table 1. Acute Toxicity Results for Technical Chlorpyrifos

STUDY	MRID Number	RESULTS	CATEGORY
Acute Oral LD_{50} - rat	Accession No. 112115	163 mg/kg M; 137 mg/kg F	II
Acute Dermal LD_{50} - rat	Accession No. 112115	202 mg/kg	II
Acute Inhalation LC_{50}; rat Supplementary	Accession No. 257590	LC_{50} > 0.2 mg/L (200 mg/m^3) (nominal concentration)	II
Eye Irritation - rabbit	Accession No. 112115	slight irritation	III
Dermal Irritation - rabbit	Accession No. 112115	slight irritation (slight hyperemia and burns that healed by 21 days)	III
Dermal Sensitization - guinea pig	00095497	non-sensitizing	NA
Acute Delayed Neurotoxicity in hens	00097144 00405106	not neurotoxic at 50, 100 or 110 mg/kg	NA

NA = not applicable

3.3 FQPA Considerations

The HED FQPA Safety Factor Committee met on November 8, 1998, February 22, 1999 and March 8, 1999 to evaluate the hazard and exposure data for chlorpyrifos and recommended that the FQPA Safety Factor (as required by the Food Quality Protection Act of August 3, 1996) be **reduced to 3x** in assessing the risk posed by this chemical. The Committee concluded that an additional safety factor is required for chlorpyrifos due to:

- concern for the extensive use of this organophosphate insecticide and resulting potential for exposure to infants and children;
- concern for the qualitative evidence of increased susceptibility at the high dose (5 mg/kg/day) in the developmental neurotoxicity study in rats based on the comparison of the severity of effects seen in the dams and pups;
- the uncertainty associated with the five-fold difference in sensitivity observed at high doses in the Moser and Padilla (1998) susceptibility study since there are no

comparable studies that examine age-related sensitivity at lower doses.

However, based on the weight-of-evidence for chlorpyrifos, the Committee recommended that the **FQPA safety factor** be **reduced** to 3x since:

- the assessments for the most significant chlorpyrifos exposures are well-characterized; actual data are available for dietary (food and water) and residential exposure assessments; acute and chronic dietary risk assessments are very refined and state-of-the-art techniques are used for some residential scenarios; where data are lacking or are incomplete for residential exposure scenarios, the DRAFT SOPs for Residential Exposure Assessments (using upper-percentile assumptions) will be used to estimate the potential exposure;

- the toxicology database is complete for assessing the effects of chlorpyrifos following *in utero* and/or postnatal exposure;

- the data submitted to the Agency under Subdivision F Guidelines provided no indication of increased susceptibility to *in utero* exposure in developmental toxicity studies and/or to pre- and post-natal exposure in reproduction studies with chlorpyrifos;

- there was no quantitative evidence of increased susceptibility in the developmental neurotoxicity study in rats;

- the qualitative evidence of increased susceptibility (developmental neurotoxicity study) was only observed at the high dose (5 mg/kg/day) and not at the effect levels for developmental and maternal toxicity;

- the five-fold difference in sensitivity (Moser and Padilla 1998 study) was observed at very high doses (15 and 80 mg/kg/day) which were the only doses tested.

The major concerns of the Committee were for the possible increased susceptibility demonstrated in young rats that cannot be discounted, coupled with the widespread use of this organophosphate insecticide and resulting potential for exposure. The exposure concerns centered on ensuring that the exposure assessments will adequately account for all potential chlorpyrifos exposures and that when relying on the chemical-specific studies submitted by the registrant, the results do not underestimate the actual potential for exposure to infants and children. The Committee agreed that if all residential exposure scenarios are assessed, either through the use of chemical-specific data or the DRAFT SOPs for Residential Exposure Assessments, the FQPA safety factor could be reduced to 3x.

The Committee determined that 3x FQPA safety factor is applicable for the following subpopulations:

Acute Dietary Assessment: The FQPA safety factor is applicable for all population subgroups due to the concern for the possible increased susceptibility of infants and children to adverse effects resulting from a single exposure to chlorpyrifos (as demonstrated in the Moser and Padilla 1998 study) coupled with the extensive use of this organophosphate insecticide and resulting potential for exposure.

Chronic Dietary Assessment: The FQPA safety factor is applicable for all population subgroups due to the concern for the possible increased susceptibility of infants and children to adverse effects resulting from repeated exposure to chlorpyrifos (as demonstrated in the developmental neurotoxicity study) coupled with the extensive use of this organophosphate insecticide and resulting potential for exposure.

Residential Exposure Assessment: The FQPA safety factor is applicable for all population subgroups due to the concern for the possible increased susceptibility of infants and children to adverse effects resulting from the extensive residential use of this organophosphate insecticide and resulting potential for exposure.

3.4 Endpoint Selection

The Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met on January 5, 1999 to evaluate the scientific quality of the two human studies for chlorpyrifos upon which the previous RfDs and dermal and inhalation endpoints were based. This re-evaluation was initiated because of a joint Science Advisory Panel/Science Advisory Board (SAP/SAB) meeting held in December 1998 that discussed issues surrounding the scientific and ethical concerns of human toxicity testing. A final SAP/SAB report has not yet been released and it is possible that these human studies will be re-assessed based on the recommendations of the SAP/SAB. The HIARC committee concluded that both human studies (Coulston et al. 1972 MRID No. 00095175, Nolan et al. 1982, MRID No. 00249203) provided useful scientific information that can be used as supportive data along with the results of animal studies. However, these studies alone are not sufficient for endpoint selection or use in risk assessment primarily because of the small sample size (n=4-6/dose group), evaluation of only one sex (men), insufficient information on study protocol, lack of control for confounding factors, and/or insufficient duration to assess chronic exposures. Subsequently, the HIARC met on February 2, 1999 and re-assessed the toxicology database to select toxicology endpoints based on animal studies for dietary and non-dietary exposure risk assessments. On February 23, 1999, the Committee re-convened to compare the results of the human and animal studies to determine the appropriate uncertainty factors (UFs) and Margins of Exposures (MOEs), respectively for dietary and non-dietary risk assessments. The Committees decisions are presented in the attached HIARC memorandum dated March 4, 1999 (D. Smegal to S. Knizner, HED Doc No. 013249).

The doses and toxicology endpoints selected by HIARC are potentially subject to further revision when policy development concerning human studies is completed and the relevant human studies have been reassessed. The doses and toxicological endpoints selected for various exposure scenarios based on animal toxicity studies with chlorpyrifos are summarized in Table 2.

Table 2
Summary of Doses and Endpoints Selected for Chlorpyrifos Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	Target MOE for Workers	Target MOE for Non-Occupational
Acute Dietary	NOAEL=0.5 UF = 100 FQPA = 3	Significant (28-40%) plasma cholinesterase inhibition at peak time of inhibition (3-6 hours post exposure) at 1 mg/kg.	Acute Blood Time Course Study in male rats	NR	NR
	Acute RfD =0.005 mg/kg/day Acute PAD = 0.0017 mg/kg/day				
Chronic Dietary	NOAEL= 0.03 UF= 100 FQPA = 3	28-54% Plasma and 6-41% RBC cholinesterase inhibition at 0.1 mg/kg/day following 2 years	2 year dog study	NR	NR
	Chronic RfD =0.0003 mg/kg/day Chronic PAD = 0.0001 mg/kg/day				
Short-Term (Dermal)	Dermal NOAEL =5	Plasma and RBC cholinesterase inhibition of 45 and 16%, respectively at 10 mg/kg/day after 4 days.	21-day dermal rat study	100	300
Intermediate- and Long-Term (Dermal)	Oral NOAEL =0.03 (3% dermal absorption)	Statistically and/or biologically significant Plasma and RBC cholinesterase inhibition at 0.1 mg/kg/day for 85-93 days to 2 year exposures	2 year dog study	100	300
Short-,and Intermediate-Term (Inhalation)	Inhalation NOAEL= 0.1	Lack of effects in 2 rat inhalation studies at the highest dose tested; 43% plasma and 41% RBC cholinesterase inhibition following oral doses of 0.3 mg/kg/day for 27 days in the developmental neurotoxicity study	Two 90 day rat inhalation studies	100	300
Long-Term (Inhalation)	Oral NOAEL= 0.03 (assume inhalation absorption is 100% of oral absorption)	28-54% Plasma and 6-41% RBC cholinesterase inhibition at 0.1 mg/kg/day following 2 years	2 year dog study	100	300

RBC = red blood cell
NR = not relevant
UF = Uncertainty Factor

MOE = Margin of Exposure
PAD = Population Adjusted Dose (includes UF and FQPA safety factor)

3.5 Endocrine Disrupter Effects

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." The Agency is currently working with interested stake holders, including other government agencies, public interest groups, and industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of the FQPA (that is, until 8/3/99) to implement this program. At that time, EPA may require further testing of chlorpyrifos for endocrine effects.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Chlorpyrifos is a broad-spectrum, organophosphate insecticide that was first registered in 1965 to control foliage- and soil-borne insect pests on a variety of food and feed crops. It is one of the most widely used organophosphate insecticides in the U.S. and is one of the top five insecticides used in residential settings. There are approximately 850 registered products containing chlorpyrifos on the market. Registered uses include a wide variety of food crops (i.e., there are approximately 112 tolerances for food and/or feed commodities such as citrus, vegetable crops, tree fruits, etc), turf and ornamental plants, greenhouses, sodfarms, as well as indoor pest control products (e.g., crack and crevice), structural pest control (e.g., termites), and in pet collars. It is used in residential and commercial buildings, schools, daycare centers, hotels, restaurants and other food handling establishments, hospitals, stores, warehouses, food manufacturing plants, vehicles, livestock premises, and mushroom houses. In addition, it is used as a mosquitocide and is registered for ear tag treatment of cattle (beef and lactating and non-lactating dairy). In 1998, Dow AgroSciences estimated that 70% of the urban chlorpyrifos use involved termite control. Chlorpyrifos products are widely used by both homeowners and PCOs.

BEAD estimates that the annual total domestic usage of chlorpyrifos is approximately 20,960,000 lbs ai for 8,027,000 acres treated. Chlorpyrifos has the largest agricultural market in terms of total pounds ai allocated to corn (26%). The largest non-agricultural markets in terms of total pounds ai applied are PCOs, termitite control (24%), and turf (12%). Crops with a high percentage of their total U.S. planted acres treated include brussel sprouts (73%), cranberries (46%), apples (44%), broccoli (41%) and cauliflower (31%).

Comprehensive lists of chlorpyrifos end-use products (EPs) and of use patterns with food/feed uses which are subject to re-registration appear are summarized in the Revised Product and Residue Chapter (Memorandum from S. Knizner to M. Hartman, May 25, 1999, D256118).

The formulations registered for use on food and feed crops include the granular (G), wettable

powder (WP), impregnated material (Impr), dry flowable (DF), and emulsifiable concentrate (EC). These formulations may be applied as foliar, bark, seed, and soil-incorporated band or broadcast treatments using ground, sprinkler irrigation, or aerial equipment. The different crop growth stages or timings as to when chlorpyrifos formulations may be applied are dormant, delayed dormant, preplant, at-planting, transplanting, postplant, post-transplant, preemergence, postemergence, and postharvest. The impregnated material formulation is registered for ear tag use on cattle. The formulations registered for animal premise treatments include the wettable powder and dry flowable. The chlorpyrifos formulations registered for food-handling establishments include the microencapsulated (Mcap), emulsifiable concentrate, and liquid ready-to-use (RTU) and soluble concentrate (SC/L) [Source: REFS search, 6/96].

4.2 Dietary Exposure

OPP has determined that TCP is not of toxicological concern and can be excluded from the tolerance expression (PP3F2884 and 3F2947 and FAP3H5396 and 3H5411/R1191, Final Rule, D.Barolo, 4/1/93). The conclusions specified in the "Tolerance Reassessment Summary" section of the Revised Product and Residue Chemistry Chapter (Memorandum from S. Knizner to M. Hartman, May 25, 1999, DP Barcode: D256118) reflect this decision and recommendation to consider only chlorpyrifos *per se* as the residue of concern.

Residue Chemistry Data Requirements

Plant and Animal Metabolism. The qualitative nature of the residue in plants and animals is adequately understood based on acceptable metabolism studies with a cereal grain (corn), a root and tuber vegetable (sugar beets), and acceptable poultry and ruminant metabolism studies. The residue of concern in plants and animals is chlorpyrifos *per se*. There are presently no direct application uses of chlorpyrifos on meat- and milk-producing animals, except for ear tag treatment of cattle (beef and lactating and non-lactating dairy).

Residue Analytical Methods - Plants and Animals. The requirements for residue analytical methods are fulfilled for purposes of re-registration. In consideration of HED's decision to regulate only the parent chlorpyrifos, acceptable methods are available for enforcement and data collection purposes. The behavior of chlorpyrifos using FDA's multi residue protocols has also been investigated and reported.

Storage Stability. The requirements for storage stability data are fulfilled for purposes of reregistration. Acceptable storage stability studies have been conducted on representative oil seeds, non-oily grains, root crops, fruits and fruiting vegetables, and low moisture content forage and hay. Additional studies have also been conducted to investigate the frozen stability of chlorpyrifos in selected processed food/feed commodities and in animal tissues and milk.

Magnitude of the Residue. The re-registration requirements for magnitude of the residue in plants (crop field trials and processed food/feed commodities) are fulfilled for the majority of crops. There are minor data gaps for asparagus, corn, cotton, crops grown solely for seed (clover and grasses), mint, peppers, sorghum, tomatoes, tree nut group and wheat. The re-registration requirements for magnitude of the residue in food-handling establishments are fulfilled. Sufficient data exist to determine that when registered formulations are used according to label directions, no detectable residues (<0.01-<0.025 ppm) are likely to occur in food items. Bait and

insecticidal strip uses would not result in residues greater than those resulting from spray applications. Therefore, the outstanding data are considered confirmatory.

The re-registration requirements for magnitude of the residue in animals are fulfilled. There are presently no registered direct application uses of chlorpyrifos on livestock animals except for ear tag treatment of cattle (beef and lactating and non-lactating dairy). An acceptable residue transfer study of chlorpyrifos to milk and cream from dairy cows wearing chlorpyrifos-impregnated tags has been submitted; data from this study indicate that residues in whole milk and fat resulting from ear tag use should not be a significant fraction of the residues resulting from intake of animal feeds containing chlorpyrifos. Cattle and poultry feeding studies have been evaluated and found adequate to satisfy feeding study requirements.

Confined/Field Rotational Crops. Provided that Dow AgroSciences modifies all labels for its chlorpyrifos containing products to limit application to 5 lb ai/A/season on those crops where rotation to another crop could occur (as was stated in their letter to the Agency dated 8/12/94), HED will not require field rotational crop studies. Furthermore, a 30 day plant back interval for rotational crops would then be appropriate.

4.3 Dietary Exposure (Food Source)

As noted previously, chlorpyrifos is registered for use on a wide variety of food crops, and has approximately 112 tolerances for food and/or feed commodities (which translates to approximately 700 food forms in the dietary analysis). Food uses evaluated in this analysis were those reflected by the established tolerances in/on raw agricultural, animal, and processed food/feed commodities for chlorpyrifos as listed in 40 CFR §180.342. Food handling establishment (FHE) tolerances were also included as cited in 40 CFR §185.1000 for the chronic dietary analysis (i.e., as a result of the registered use in FHE, all foods have an established tolerance of 0.1 ppm, unless they are covered by higher tolerances). The tolerances published for chlorpyrifos under 40 CFR §180.342, 185.1000 and 186.1000 have been reassessed (HED Revised Product and Residue Chemistry Chapter, memorandum from S. Knizner to M. Hartman, D256118, May 25, 1999). The established tolerances in/on raw agricultural, animal, and processed food/feed commodities are expressed either in terms of the combined residues of chlorpyrifos and its metabolite 3,5,6-trichloro-2-pyridinol (TCP) **or** as chlorpyrifos *per se*. HED has determined that TCP is not of toxicological concern and concluded that TCP can be excluded from the tolerance expression. Reassessed tolerances are in terms of chlorpyrifos *per se*. Thus, for purposes of this analysis, only residues of chlorpyrifos *per se* were considered, when data were available. Whenever possible, data for anticipated residues (ARs) reflect levels of chlorpyrifos *per se*.

The refined Tier 4 acute and chronic dietary exposure assessments were conducted using the Dietary Exposure and Evaluation Model (DEEM™) system. DEEM can be used to estimate exposure to residues in foods comprising the diets of the U.S. population, including population subgroups. The software contains food consumption data from the USDA Continuing Survey of Food Intake by Individuals (CFSII) from 1989-1992. For chronic dietary risk assessments, the 3-day average of the consumption data for each sub-population is combined with average residues in commodities to determine the average exposure in mg/kg/day. For acute dietary risk assessment, the entire distribution of single day food consumption events is combined with a distribution of residues (probabilistic analysis, referred to as "Monte Carlo") to obtain a

distribution of exposures in mg/kg/day.

For chlorpyrifos, inputs to the DEEM analysis include Dow AgroSciences' 1993 National Food Survey (NFS, also known as the market basket survey data), U.S. Department of Agriculture's Pesticide Data Program (PDP) monitoring data (1994-1997), the Food and Drug Administration (FDA) Surveillance Monitoring Program data (1992-1997), and to a much lesser extent, field trial residue data, and percent crop treated data (BEAD Quantitative Usage Analysis for chlorpyrifos dated 5/11/99). Where percent crop treated estimates indicated no chlorpyrifos use, a default minimum assumption of 1% crop treated was applied. Where residues were nondetectable, one-half the limit of detection (LOD) was assumed. All available processing factors were incorporated into the dietary exposure analysis.

The Reference Dose (RfD) is derived from an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control, along with the application of uncertainty factors. The percent of the RfD is calculated as the ratio of the exposure value to the RfD (exposure/RfD x 100 = % RfD). The population adjusted dose (PAD) is the adjusted RfD reflecting the retention or reduction of the FQPA safety factor for all populations. For chlorpyrifos, the population adjusted doses pertaining to acute and chronic dietary exposure are 0.0017 mg/kg/day and 0.0001 mg/kg/day, respectively. Exposures less than 100% of the PAD do not exceed HED's level of concern.

4.3.1 Acute Dietary Exposure Assessment

Dow AgroSciences has submitted a Tier 4 probabilistic acute dietary risk assessment that incorporates data from their NFS for nine commodities (all highly consumed by children), and residue field trial data for all other commodities (MRID No. 44403301, October 1997). OPP currently evaluates probabilistic assessments at the 99.9th percentile of exposure. HED evaluated the Dow AgroSciences' October 1997 dietary analysis in memorandum from C. Christensen to D. Smegal, D242040, December 16, 1998. Subsequently, Dow AgroSciences refined their exposure estimates based on discussions with the Agency in November 1998 and submitted refined dietary estimates on December 15, 1998, and January 13, 1999. HED reviewed the most recent Tier 4 refined dietary estimates of January 13, 1999 (memorandum from H. Bolles of Dow to HED) and concluded that these estimates still exceed HED's level of concern for several child population subgroups, and the U.S. population (i.e., > 100% of the aPAD). The results of the most recent Tier 4 dietary analysis conducted by Dow AgroSciences (January 13, 1999) are presented on Table 3. Consequently, HED conducted Tier 3/4 and 4 acute probabilistic dietary exposure analyses of chlorpyrifos that incorporate additional monitoring data from PDP and FDA that the Registrant submissions did not include.

The HED Tier 3/4 and 4 dietary assessment incorporated the most highly refined techniques recently developed (i.e., "decomposition" of monitoring data). As noted previously, HED used PDP, and FDA monitoring data, in conjunction with the Dow AgroSciences' NFS to the greatest extent possible for this assessment. Samples analyzed in the NFS include fresh apple, applesauce, apple juice, orange juice, peanut butter, whole milk, ground beef, pork sausage, and tomatoes. Where available, the PDP data were used in preference to the FDA data. The distinguishing factor between a Tier 3 and 4 assessment is the inclusion of NFS data. For this analysis, HED conducted two probabilistic acute dietary exposure estimates: a Tier 4 estimate which utilized

the data for all 9 commodities included in Dow AgroSciences' NFS, along with PDP and FDA monitoring data; and a Tier 3/4 estimate which only incorporated data for 2 commodities from the NFS (beef and pork) and PDP and FDA monitoring data for other commodities. In both analyses, field trial data were used for a total of seven commodities (field corn, soybeans, cottonseed, cranberries, beans, sunflowers, and sugarcane). Dow conducted their probabilistic Tier 4 acute dietary exposure estimate using data from the NFS and residue field trial results for all other commodities. Details of HED's acute dietary risk assessment are presented in memorandum from C. Christensen and D. Soderberg to M. Hartman, July 22, 1999.

The NFS data supplied by Dow represent are now somewhat dated as compared to PDP and FDA data (samples were collected in 1993) and are limited (200 samples for most commodities). For some commodities included in the NFS, more recent and extensive data are available from monitoring programs. For example, the NFS included 200 apple samples, but PDP collected 1908 samples from 1994-1997 and FDA collected 1342 samples from 1992-1997. Because of the limited and dated (relative to PDP and FDA monitoring data) NFS data, the Agency elected to conduct a Tier 3/4 analysis, which only incorporated NFS data for beef and pork, because those are the best data available for meat. The Agency believes that the Tier 3/4 exposure and risk estimate most accurately reflects current dietary exposures.

Because monitoring data usually are derived from samples that are composites of multiple units of produce, such samples were "decomposited" for the purpose of estimating single serving acute exposure. In addition, because the current decompositing procedure may cause some projected residue values to exceed tolerances, the results were truncated at tolerance levels for the purpose of this assessment. Only three commodities had a few samples truncated at tolerance levels: fresh peaches (26 samples); sweet potatoes (30 samples); and tomatoes (8 samples).

Exposure (consumption x residues) was compared to an acute population adjusted dose of 0.0017 mg/kg/day. The acute dietary risk analysis estimates the distribution of single day exposures for the overall U.S. population and certain subgroups. The analysis evaluates exposure to the chemical for each food commodity.

Table 3 summarizes the acute probabilistic dietary risk estimates for the U.S. Population and most highly exposed sub-populations. For comparison purposes, Dow AgroSciences' Tier 4 acute dietary exposure estimates are also presented. As shown in Table 3, for all exposure dietary exposure analyses (Dow's and the Agency's), at the 99.9th percentile, exposure estimates for the most highly exposed subgroup, children 1 - 6 years old, were greater than 100% of the aPAD. Risk estimates ranged from 120% (Agency Tier 4 estimate) to 190% (Dow Tier 4 estimate) of the aPAD. These risk estimates exceed HED's level of concern. For the U.S. population and all other sub-populations, HED Tier 3/4 and Tier 4 exposure estimates at the 99.9th percentile were less than 100% of the aPAD, and therefore these risks do not exceed HED's level of concern. At the 99th percentile, all exposure estimates for all population subgroups were less than 100% of the aPAD.

Table 3. Summary of Chlorpyrifos Acute Dietary Probabilistic Exposure Analysis (Tier 4) by DEEM (99.9th Percentile).						
Population	Dow AgroSciences Tier 4 Estimate (a)		Agency Tier 3/4 Estimate (b)		Agency Tier 4 Estimate (c)	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
U.S. Population	0.001922	110	0.000953	56	0.000737	44
All Infants <1 year	0.001080	64	0.001337	79	0.000738	43
Nursing Infants <1 year	0.001843	110	0.001497	88	0.000979	58
Non-nursing Infants <1 year	0.000574	34	0.001285	76	0.000722	43
Children 1-6 years	0.003285	190	0.002790	160	0.002103	120
Children 7-12 years	0.002135	130	0.001243	73	0.000973	57
Females 13+/nursing	Not reported		0.001112	65	0.000338	61

(a) Includes use of NFS data and field trial results (MRID #44403301). Results as presented in Dow's letter to the Agency dated 1/13/99 (H. Bolles to EPA, HED).

(b) Includes use of monitoring data and NFS for beef and pork.

(c) Includes use of monitoring data and NFS data for all 9 commodities included in the survey.

HED is also performing a critical exposure contribution analysis to determine if there are any individuals with excessive consumption patterns that affect the risk estimates. This analysis has not been completed.

The uncertainties in the acute dietary exposure estimates are discussed below following the chronic dietary exposure assessment discussion.

4.3.2 Chronic Dietary Exposure Assessment

A refined chronic exposure analysis was performed using the DEEM ™ exposure modeling software. HED conducted both Tier 3/4 and Tier 4 chronic dietary assessments, similar to the acute dietary assessments. The input values for the Tier 3/4 and Tier 4 analyses included the PDP, FDA and Dow AgroSciences NFS data, in addition to average residues from field trials and incorporated percent of the crop treated information from BEAD. For the Tier 3/4 assessment, NFS data from only two commodities (ground beef and ground sausage) were used, while the Tier 4 assessment incorporated NFS data for all nine commodities. The primary difference between the Tier 3/4 and Tier 4 analyses is the residue data used for apples. Exposure (consumption) was compared to the chronic population adjusted dose (cPAD) of 0.0001 mg/kg/day. A summary of the residue information included in this analysis can be found in the attached memorandums from D. Hrdy to M. Hartman, June 1, 1999, D255451 and D255451.

As shown in Table 4, the Tier 3/4 chronic dietary residue contributions without the food handling establishment use are 107% and 102% of the cPAD for most highly exposed subgroups, non-nursing infants and children 1-6, respectively, and therefore, exceed HED's level of concern. Risk estimates for all other population subgroups, including the U.S. population for the Tier 3/4 assessment, and all population subgroups for the Tier 4 assessment were less than 100% of the cPAD, and therefore, do not exceed HED's level of concern. For the Tier 3/4 and Tier 4 assessments, the chronic dietary residue contribution, with the food handling establishment use

included, is 210-278% of the cPAD for the U.S. population and 790-952% of the cPAD for the most highly exposed subgroup, non-nursing infants (< 1 yr), and also exceeds HED's level of concern. For the Tier 3/4 assessment (without the food handling establishment use), the commodities that contribute most to the dietary risks for non-nursing infants are soybeans, protein isolate (34.8%), corn grain (15.2%), apples (13.6%), dairy products (12%), and apple juice concentrate (3.8%). For the Tier 3/4 assessment (without the food handling establishment use), the commodities that contribute most to the dietary risks for children 1-6 years of age are dairy products (24.4%), wheat flour (15%), apples (9.6%), corn grain (9.5%) and apple juice (4.7%).

Table 4
Summary of Chlorpyrifos Chronic Dietary Exposure Analysis by DEEM

Population Subgroup	Tier 3/4 Excludes Food Handling Establishment Use (a)		Tier 3/4 Includes Food Handling Establishment Use (a)		Tier 4 Excludes Food Handling Establishment Use (b)		Tier 4 Includes Food Handling Establishment Use (a)	
	Exposure (mg/kg BW/day)	%cPAD	Exposure (mg/kg BW/day)	%cPAD	Exposure (mg/kg BW/day)	%cPAD	Exposure (mg/kg BW/day)	%cPAD
US Population	0.000048	48.4	0.00028	278	0.000019	19.5	0.00021	210
Western Region	0.000052	51.6	0.00029	287	0.000021	21.3	0.000217	217
Non-Hispanics/ Non-White/Non Black	0.000065	65	0.00031	312	0.000021	21	0.000226	226
All infants (< 1 yr)	0.000084	83.9	0.00075	749	0.000022	21.9	0.000627	627
Non-nursing Infants (< 1 yr)	0.000107	107	0.00095	952	0.000025	25.2	0.00079	790
Children (1-6 years)	0.000102	102	0.00056	557	0.000052	51.8	0.000414	414
Children (7-12 years)	0.000066	65.8	0.00036	355	0.000031	31.2	0.000258	258
Females 13+, nursing	0.000059	59.3	0.00029	289	0.000025	24.5	0.000216	216

(a) Includes use of monitoring data and NFS for beef and pork.
(b) Includes use of monitoring data and NFS data for all 9 commodities included in the survey.

Uncertainties of Dietary Exposure Estimates

The Agency believes that the Tier 3/4 risk assessment presented is the most refined to date for acute dietary exposure to chlorpyrifos. However, there are some uncertainties associated with this exposure estimate as follows.

(a) For a number of commodities for which no chlorpyrifos tolerances have been established, PDP has found residues in more than one year of sampling. These include spinach, squash, and carrots as shown below:

Commodities Frequently Fed to Infants and Children that Lack Established Chlorpyrifos Tolerances, but Have Detected Residues in PDP

Commodity	Year	# Samples with Detections	% Samples with detections	Minimum Residue Detected (ppm)	Maximum Residue Detected (ppm)
Carrots	1994	2	0.3	0.005	0.005
	1995	6	0.9	0.005	0.019
	1996	7	1.4	0.005	0.074
Spinach	1995	46	7.5	0.005	0.11
	1996	26	5.0	0.003	0.030
	1997	11	2.1	0.005	0.026
Squash	1997	4	1.8	0.005	0.005

Residues were also detected in celery (4 samples in 1994, 0.005 - 0.045 ppm), potatoes (1 sample in 1994, 0.024 ppm), and lettuce (1 sample in 1994 at 0.01 ppm). These residue results were not included in the Agency's dietary exposure assessment as they represent misuse of chlorpyrifos. However, because these violations have occurred over the years, excluding them might have under-represented potential dietary exposure, especially for infants and children. Therefore, an additional set of dietary exposure assessments have been performed including results for squash, spinach and carrots - three commodities frequently fed to infants and children. Celery, lettuce and potatoes were not included. These additional assessments were not significantly different from the original assessments.

(b) The consumption database used in the dietary exposure analysis (CSFII, 1989-1992) has a limited number of individuals in the age group infants less than one year old. The USDA is currently conducting the Supplemental Children's Survey (approximately 5000 children). The results of this supplemental survey are expected in December 1999.

(c) The dietary exposure analyses relied primarily on monitoring data obtained either "at the farmgate" in the case of FDA or in regional distribution warehouses for PDP data. The NFS results are for samples obtained at supermarkets, but only represent one year of data. Residues potentially present on items purchased at roadside produce stands or farmer's markets are not represented in this analyses.

(d) Potential exposure to chlorpyrifos residues from consumption of fish was not addressed.

No tolerances for fish are currently established. In 1992 the Agency Office of Water (OW) published a report (EPA 1992) that summarized chlorpyrifos residues found in freshwater fish at that time. The primary focus of the study was monitoring for dioxin/furan in fish. However, chlorpyrifos residues were detected in 26% of the 388 sites tested, with median, mean, and maximum concentrations of non-detect, 4.09, and 344 ppb respectively. This study indicated that consumption of freshwater fish could contribute to dietary exposure to chlorpyrifos. FDA also has monitored fish for chlorpyrifos. Of all fish and crustacean samples tested between 1992 to 1998, FDA found residues of chlorpyrifos in one trout (1994) and twelve catfish (four catfish in each year 1992 - 1994). FDA has found no detectable residues of chlorpyrifos in any fish from 1995 to 1998.

(e) No cooking factors could be incorporated in this dietary exposure analysis. If Dow has any such data they should be supplied to the Agency (this was noted in a memo from HED (S. Knizner) to Dow on 4/7/95). If reduction of residues is noted upon cooking, this could lead to lower acute dietary exposure estimates.

(f) The NFS data supplied by Dow are now somewhat dated (samples were collected in 1993) in comparison to more recent PDP and FDA data, and are limited (200 samples). For some commodities included in the NFS, more recent and extensive data are available from monitoring programs. For example, the NFS included 200 apple samples, but PDP collected 1908 samples from 1994-1997 and FDA collected 1342 samples from 1992-1997. Because of the limited and dated NFS data, the Agency elected to conduct a Tier 3/4 analysis, which only incorporated NFS data for beef and pork, because those are the best data available for meat.

Chlorpyrifos Screening-Level Exposures and Risks from Freshwater Fish Consumption

In 1992, the EPA Office of Water (OW) published a report that summarized the chlorpyrifos residues in freshwater fish, and evaluated the health risks to individuals that consume freshwater fish as part of a National Screening Assessment (EPA 1992). The results of the EPA OW Assessment were not included in HED's dietary analysis because of the screening-level nature of this investigation (i.e., limited fish samples collected in areas of chlorpyrifos use, and a greater focus on bottom feeding fish such as carp and white sucker that do contribute significantly to the diet). Nevertheless, this study indicates that consumption of freshwater fish could also contribute to the dietary exposures and risks of chlorpyrifos. The results of this assessment are presented below.

In the OW study, game and bottom feeding fish were collected from 388 sites, of which 314 were near point and non point sources of pollution, 39 locations were from the U.S. Geological Survey (USGS) National Stream Quality Accounting Network (NASQAN), and 35 locations represented background levels. The selection of sites was biased toward sites where dioxin/furan concentrations in fish are expected (i.e., near pulp and paper mills and industrial sources), because the original intent of study was to investigate these compounds. Consequently, few of the sites (n=15) investigated were near agricultural areas, where chlorpyrifos use is pervasive.

Chlorpyrifos was detected in fish from 26 percent of the 388 sites, with median, mean and maximum concentrations of non detect, 4.09 and 344 μg/kg (ppb), respectively. (The second highest concentration was 64.5 μg/kg). Over 70 percent of the fish concentrations at all sites

were below detection. The highest concentrations were observed primarily in bottom feeding fish such as carp near agricultural facilities. The mean concentration from agricultural areas was 24.46 μg/kg. In general, chlorpyrifos concentrations were detected in whole-body samples of bottom feeders and in fillet samples of game fish at roughly the same average concentration.

Health risks were calculated using fillet samples of game fish collected from 106 sites. Risk estimates were calculated using standard EPA risk assessment procedures, an average fish consumption rate of 6.5 g/day for the U.S. population, and the chlorpyrifos RfD on EPA's Integrated Risk Information System (IRIS) of $3x10^{-3}$ mg/kg/day (which is an order of magnitude higher than the RfD developed by HED). The resulting hazard indices associated with ingestion of the maximum and mean chlorpyrifos fillet concentrations were $2.4x10^{-3}$ and $6.4x10^{-5}$, respectively for the U.S. population. These risk estimates are both < 1% of the EPA RfD on IRIS, and would represent 7.2% and < 1% of the HED chronic PAD, respectively.

4.3.3 Dietary Exposure (Drinking Water Source)

The Environmental Fate and Effects Division (EFED) conducted a drinking water assessment for chlorpyrifos based on an analysis of existing ground and surface water monitoring data in conjunction with Tier 1 and Tier 2 modeling (using GENEEC 1.2, PRZM 2.3-EXAMS, and SCI-GROW) (Attached memo from M. Barrett to S. Knizner, November 13, 1998). EFED also provided drinking water estimates for the primary degradate, TCP, which are predicted to be higher than chlorpyrifos levels. However, TCP, is not of toxicologic concern and is not included in the chlorpyrifos tolerance (memo from A. Levy to D. Edwards, 11/29/88). The drinking water exposure estimates are discussed in greater detail below by water source.

The available environmental fate data suggest that chlorpyrifos has a low potential to leach to groundwater from most typical agricultural uses in measurable quantities, except following termiticide use. Chlorpyrifos is persistent in concentrated applications used in termiticide treatments. Although limited, the available data indicate that the primary metabolite of chlorpyrifos, 3,5,6-TCP is more mobile, and significantly more persistent in many soils, especially under anaerobic conditions.

4.3.3.1 Groundwater Exposure Levels

EFED conducted an analysis of over 3000 groundwater monitoring data available in U.S. Geological Survey's National Water Quality Assessment (NAWQA) Program databases, and in EFED's Pesticides in Ground Water Data Base (PGWDB). Chlorpyrifos was infrequently detected in groundwater (< 1% of the 3000 wells). The majority of concentrations were reported to be <0.01 μg/L, with only occasional contamination at a maximum level of 0.04 μg/L. Although the available monitoring data represent a large part of the U.S., it is not clear that they represent the most vulnerable groundwater where chlorpyrifos is used most intensively. The Pesticides in Ground Water Database (PGWDB) reports a maximum detected concentration of 0.65 μg/L.

EFED also performed screening-level model estimates of chlorpyrifos concentrations in groundwater using SCI-GROW. The estimated upper-bound, 99+ percentile concentration for chlorpyrifos in groundwater using the SCI-GROW screening model is 0.11 μg/L for sweet corn use. Therefore, based on an analysis of both monitoring and modeling data, EFED concludes the

large majority of the country (>99%) will not have potable groundwater that contains chlorpyrifos at levels greater than 0.1 μg/L. This concentration is recommended to evaluate both acute and chronic exposures. The NAWQA monitoring data support that the SCI-GROW modeling estimate is conservative.

Chlorpyrifos exposure from termiticidal use is highly localized and usually only in wells located within 100 feet of the treatment area. For this use, the maximum detected concentration is 2000 μg/L, with unknown chronic exposure levels that are presumably significantly lower, but that can persist at detectable levels for at least 6 months. EFED recommends a value of 2000 μg/L to evaluate both acute and chronic groundwater exposures following termiticide use. Chlorpyrifos use as a termiticide is significant, with a recent estimate of seven million pounds constituting about 30% of the total annual use. Dow AgroSciences states that this exposure only occurs in homes where the well casing has a crack in it, and the well is near or in the foundation. HED has determined that the Label Improvement Process for Termiticides (PR notices 96-7 for termiticides) will reduce this exposure in the future.

4.3.3.2 Surface Water Exposure Levels

EFED conducted an analysis of 20 NAWQA study units for flowing surface water collected from rivers and streams over the last several years. Chlorpyrifos was detected at frequencies up to 26% of 604 samples from the 20 NAWQA study sites in 1997 and in 65% of 57 samples from Georgia, Alabama and Florida in 1994. The maximum reported dissolved chlorpyrifos concentration in surface water was 0.4 μg/L, with the majority of chronic concentrations < 0.1 μg/L. EFED notes that although the available monitoring data represent a large part of the U.S., the monitoring data may not represent the most vulnerable watersheds where chlorpyrifos use is pervasive. EFED notes that a limited number of watersheds in the U.S. may have chlorpyrifos concentrations higher than 0.4 μg/L due to higher usage rates or greater pesticide runoff. In particular, acute exposure levels could be higher for streams draining watersheds with more intense chlorpyrifos use. EFED also notes that there are no significant data for lakes and reservoirs.

EFED also performed screening-level model estimates of chlorpyrifos concentrations in surface water such as lakes and reservoirs using Tier I GENEEC or Tier II PRZM/EXAMS. Inputs to the models included high exposure agricultural scenarios for major crops (alfalfa, corn, citrus, and tobacco) at the maximum application rates. Estimated average and peak concentrations of chlorpyrifos in surface water using the PRZM/EXAMS screening model were 6.7 μg/L and 31 μg/L, respectively. The maximum peak estimated environmental concentration (EEC) of 31 μg/L, is based on a pond draining an adjacent 100% treated field model (it is highly unlikely that 100% of a watershed constituting a major drinking water source would be treated with chlorpyrifos in a given year).

Based on an analysis of the monitoring and modeling data, EFED recommends using the maximum detected chlorpyrifos concentration in filtered samples of 0.4 μg/L for flowing surface water of all sizes as a high estimate of the typical concentration for acute and chronic exposure. EFED concluded that the 0.4 μg/L estimate (a high acute exposure level for streams) is more reasonable than the conservative PRZM/EXAMS maximum peak EEC of 31 μg/L for lakes and reservoirs. This is because multi-month or annual mean concentrations in a reservoir are expected to be less than the maximum reported concentrations in the flowing water feeding the

reservoir. The monitoring data also demonstrate that chronic concentrations of chlorpyrifos are unlikely to exceed 0.1 μg/L. However, since monitoring data are not available for the most vulnerable watersheds, EFED recommends using 0.4 μg/L for chronic exposures (for all surface water). These estimates only apply to drinking water because residues of lipophilic pesticides, such as chlorpyrifos, bound to sediment and suspended solids could contribute to exposure following consumption of unfiltered water.

4.3.3.3 Drinking Water Exposure Concentrations

Because monitoring data are available, HED calculated estimated environmental exposure levels and risks for chlorpyrifos in surface and groundwater. Table 5 summarizes the estimated dose to adults and children, resulting from ingestion of drinking water containing the EFED-recommended chlorpyrifos drinking water estimates.

Table 5
Drinking Water Exposure Estimates for Chlorpyrifos

Drinking Water Source	Concentration (μg/L)		Estimated Dose (μg/kg/day) (a)		
	Acute	Chronic	Adult Male	Adult Female	Child
Groundwater, except where termiticidal application occurs	0.1		0.0029	0.0033	0.01
Groundwater, termiticide use areas	2000		57	67	200
Surface water, streams and rivers	0.4		0.011	0.013	0.04
Surface water, reservoirs and lakes	0.4 to 31	0.4 to 6.7	0.011 (b)	0.013 (b)	0.04 (b)

(a) Exposure for both acute and chronic durations. Exposure (μg/kg/day) = (Conc (μg/L) * water ingestion (L/day)) / Body weight (kg). Assumes the following body weights: 70 kg for adult male, 60 kg for adult female and 10 kg for child. Assumes that adults ingest 2 L of water per day and that a child ingests 1 L of water per day.
(b) Exposures calculated assuming 0.4 μg/L, which is the concentration recommended by EFED for both the acute and chronic risk assessments.

In comparison, the one-day, 10-day, and longer-term USEPA health advisories for a 10-kg child are 30 μg/L. The lifetime health advisory for a 70-kg adult has been established at 20 μg/L; the adult longer-term health advisory is 100 μg/L.

EFED notes that there are significant uncertainties associated with the drinking water estimates which are as follows:

(1) The estimates are intended to be as realistic as possible but apply only to the most vulnerable populations because existing monitoring data imply that the majority of the U.S. population will not be exposed at these levels;

(2) All of these estimates are for unfinished water, and could be lower in finished drinking water that has been treated (i.e., activated charcoal would reduce chlorpyrifos levels); and

(3) The exposure estimates are highly conservative (i.e., exceed actual exposure by several-

fold) for the majority of the U.S. population, based on the existing monitoring database, which covers a large part of the U.S. However, chlorpyrifos residues in surface waters could be much higher in some areas where chlorpyrifos usage is more pervasive in the watershed.

Table 6 summarizes the acute and chronic risks from drinking water exposure to chlorpyrifos.

Table 6
Acute and Chronic Risk from Drinking Water Exposure to Chlorpyrifos

Drinking Water Source	Concentration (μg/L) (a)	Percent Acute PAD (b)			Percent Chronic PAD (c)		
		Adult Male	Adult Female	Child	Adult Male	Adult Female	Child
Groundwater, except where termiticidal application occurs	0.1	0.17	0.2	0.6	2.9	3.3	10
Groundwater, termiticide use areas	2000	3400	3900	12000	57000	67000	200000
Surface water, streams, rivers, reservoirs and lakes	0.4	0.67	0.78	2.4	11	13	40

(a) Concentrations for both acute and chronic exposures recommended by EFED.
(b) Acute PAD is 0.0017 mg/kg/day, which is comprised of the acute RfD of 0.005 mg/kg/day, with inclusion of the 3x FQPA safety factor.
(c) Chronic PAD is 0.0001 mg/kg/day, which is comprised of the chronic RfD of 0.0003 mg/kg/day, with inclusion of the 3x FQPA safety factor.

As shown on Table 6, acute exposure to the EFED- recommended chlorpyrifos concentrations in ground and surface water, except for termiticide use, represent less than 3% of the aPAD, while chronic exposures represent up to 40% of the cPAD for children. Exposure to the chlorpyrifos ground water concentrations resulting from termiticide use for either acute or chronic durations, however, would result in exposures that exceed 100% of the aPAD and cPAD, and therefore, exceed HED's level of concern.

4.3.3.4 DWLOCs for Acute, Short-, and Intermediate-Term and Chronic (Non-Cancer) Exposure

Currently, HED uses Drinking Water Levels of Comparison (DWLOCs) as a surrogate to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light of the total aggregate exposure to that pesticide from food, water, and residential uses. It is used as a point of comparison against the model estimates to determine if the estimated concentration is of concern. A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations. DWLOCs were not calculated for chlorpyrifos because the acute and chronic dietary risks, as well as the short-, intermediate and long-term residential postapplication risks alone exceed HED's level of concern. Therefore, in effect, the DWLOCs would be zero. In addition, because monitoring data are available for chlorpyrifos, conservative risk estimates based exclusively on ground and surface water exposures, as a percentage of the acute and chronic PAD were calculated as shown on Table 6.

4.3.4 Typical Chlorpyrifos Baseline Exposure in the U.S. Population

Because of chlorpyrifos' extensive use on food and in homes and the workplace, the majority of the U.S. population is exposed to this pesticide. Literature studies, in addition to several of the registrant-submitted biomonitoring studies, have estimated typical or baseline exposure to chlorpyrifos by measuring the urinary excretion of 3,5,6-TCP, the primary metabolite of chlorpyrifos and chlorpyrifos-methyl.

The study published by Hill et al. (1995) measured the biomarker 3,5,6-TCP in 993 adults (20-59 years old) participating in the National Health and Nutrition Examination Survey III, known as NHANES III from 1988 - 1994. The individuals were selected from a broad spectrum of the U.S. population reflecting both sexes and different age groups, races/ethnicities, urban/rural residences and regions of the country. 3,5,6-TCP was detected in 82% of the individuals evaluated. The results of NHANES III differ significantly from the NHANES II survey collected between 1976 and 1980, where only 5.8% of the 6990 people evaluated had concentrations of 3,5,6-TCP greater than the detection limit of 5 μg/L. In the NHANES III survey, 31% of the 993 people had 3,5,6-TCP concentrations greater than 5 μg/L. It should be noted however, that the lower detection limit of 1 μg/L in the NHANES III study could partially account for the increased frequency of detection of 82%. The results of this study are presented below in Table 7.

The Minnesota Children's Pesticide Exposure Study, which is one of the National Human Exposure Assessment Surveys (NHEXAS), evaluated 89 children ages 3-12 (mean 7.6 ± 2.9 yrs), stratified by those with more frequent residential insecticide usage (personal communication with James Quackenboss, March 1, 1999). This study was initiated to assess children's actual exposures to pesticides. The study examined the relationship between environmental concentrations and urinary biomarker levels of 3,5,6-TCP from a population-based study of total exposure in urban and rural children. Monitoring of tap water, personal, indoor, and outdoor air, house dust, soil, food and beverages was conducted over 6 days. Urine samples were obtained for 87% of the study subjects. Preliminary data were presented at the International Society for Environmental Epidemiology (ISEA) conference in Boston in August 1998 (Adgate et al. 1998). The final study results are anticipated to be available in April 2000. The results from the metabolite analysis suggest that these children have higher concentrations of 3,5,6-TCP than was reported for the NHANES-III adult population (medians of 8 and 2 μg/L TCP, respectively) (Quackenboss et al. 1998). In the study, 30% of the households had used chlorpyrifos.

Dow AgroSciences recently conducted four biomonitoring studies to quantify exposures to residential populations following the use of chlorpyrifos products in the home. Volunteers were typically adults of both sexes between the ages of 25 and 65. Other details were not provided (i.e., ethnicity). For all of these studies, baseline chlorpyrifos exposures of the volunteers were quantified by analysis of urinary 3,5,6-TCP prior to commencement of the study. Quantification of baseline chlorpyrifos exposure for each volunteer was necessary in order to determine actual exposure associated with a product's use. For each of these studies, baseline TCP measurements were subtracted from total TCP measurements to quantify chlorpyrifos exposure in the biomonitoring study. In addition, residents were instructed to avoid chlorpyrifos exposure for several days (typically one week to 10 days) prior to the measurement of baseline levels. Therefore, the baseline exposures are most likely attributed to dietary exposure of chlorpyrifos and chlorpyrifos-methyl.

Table 7 summarizes the typical baseline exposure estimated from the Hill et al. (1995) and Dow AgroSciences biomonitoring studies. All exposure estimates have been normalized for creatinine excretion. The assumptions and equations are presented in the footnotes.

Table 7
Typical Chlorpyrifos Baseline Exposure Estimates

Source/Study	*Sample Size*	*Percent with TCP in urine*	*Mean Chlorpyrifos Dose (a) µg/kg/day*	*Range of Chlorpyrifos Dose µg/kg/day*
Residential Biomonitoring Studies				
Residential exposures from Lawn treated with Chlorpyrifos Spray (MRID 43013501)	8	100%	0.3	0.09 - 0.6
Residential Exposures from Lawn treated with Granular Chlorpyrifos (MRID 44167101)	9	100%	0.5	0.21 - 1.47
Residential Exposure from Crack and Crevice Application (MRID 44458201)	6	100%	0.4	0.1-0.86
Residential Exposures from Application of a Ready-to-Use Formulated Product (MRID 44739301)	15	100%	0.12	0.05-0.3
Literature Studies				
Hill et al. 1995 (NHANES III)	993	82%	0.2 (b)	ND - 2 (b)

ND = not detected

(a) Based on pre-study 3,5,6-TCP results in urine. See HED study reviews for details.

(b) Creatinine adjusted concentrations of mean 3.1and maximum of 34 µg TCP/g creatinine, respectively that assumes an average creatinine excretion rate of 1.8 g/day (Tietz 1982), a body weight of 70 kg, and that 72% of chlorpyrifos is excreted in the urine. A molecular weight adjustment was also made 350.6 chlorpyrifos/ 198 TCP. Assumes steady-state between exposure and excretion. Example calculation: Dose (µg/kg/day) = [(3.1 µg TCP/g creatinine * 350.6/198 * 1.8 g/day) / (70 kg * 0.72 (fraction chlorpyrifos excreted as TCP)].

4.4 Non-Dietary Exposure

Chlorpyrifos is an organophosphate insecticide used extensively in residential settings by both residents and PCOs, and for agricultural use (e.g., citrus, vegetable crops, tree fruits, etc.), greenhouse uses, outdoor ornamental uses, and sodfarm uses. It is one of the top five insecticides used in residential settings. There are approximately 850 registered products containing chlorpyrifos on the market. Registered uses include a wide variety of food, turf and ornamental plants, as well as indoor products, structural pest control, and in pet collars. It is used in residential and commercial buildings, schools, daycare centers, hotels, restaurants, hospitals, stores, warehouses, food manufacturing plants and vehicles. In addition, it is used as a mosquitocide. In 1998, the Dow AgroSciences estimated that 70% of the urban chlorpyrifos use involved termite control.

Chlorpyrifos, is formulated as a wettable powder (containing 50% a.i.), emulsifiable concentrates (41.5-42.8%), dust (containing 0.1-7% a.i.), granular (containing 0.075%-15% a.i.), bait (containing 0.5% a.i.), flowables (containing 30% a.i.), impregnated material (containing 0.5-10% a.i.), pelleted/tableted (containing 0.5-1.0% a.i.), pressurized liquids (0.9-3.8% a.i.), and

microencapsulated (0.5-2.5% a.i.). According to Dow AgroSciences, formulations with concentrations greater than one pound a.i. per gallon (approximately 13% a.i.) are sold to licenced pest control or turf and ornamental professionals only. Lower concentrations are available to homeowners from other suppliers for over-the-counter purchase. Except aerosols, granules and dusts, all formulations for application are diluted in water to a concentration of 1 percent a.i. or less (Dow AgroSciences 1998).

Occupational and residential exposures to chlorpyrifos can occur during handling, mixing, loading and applying activities. Occupational postapplication exposure can occur for agricultural workers during scouting, irrigation and harvesting activities. Residential postapplication exposure can occur following treatment of lawns, or residences for cockroaches, carpenter ants, termites, and other insects. In addition, there is a potential for inadvertent oral exposure to children from eating chlorpyrifos-treated turf and soil. Postapplication exposure to children can occur in locations other than the home, including schools, daycare centers, playgrounds, and parks. There is insufficient use information and exposure data to assess exposure resulting from use in vehicles (i.e., planes, trains, automobiles, buses, boats) and other current label uses such as treatment of indoor exposed wood surfaces, supermarkets, theaters, furniture, and draperies. However, HED has concern for these uses based on the scenarios assessed within this document.

Based on toxicological criteria and potential for exposure, HED has conducted dermal and inhalation exposure assessments for the occupational and residential handlers, occupational postapplication, in addition to residential postapplication dermal, inhalation to adults and children and inadvertent oral exposure to children.

Details of the agricultural and/or greenhouse exposure scenarios are presented in the attached memorandum from T. Leighton to D. Smegal/M. Hartman, D257954, July 22, 1999. Details of the occupational/residential handler assessment for residential settings and the postapplication residential risk assessment are presented in the attached memorandum from D. Smegal to M. Hartman, D254880, June 30, 1999.

4.4.1 Occupational Handler Exposure Scenarios

HED has identified 25 major exposure scenarios for which there is potential occupational handler exposure during mixing, loading, and applying products containing chlorpyrifos to agricultural crops and/or greenhouses (16 scenarios) and to non-agricultural use sites (9 scenarios) such as residential settings. These occupational scenarios reflect a broad range of application equipment, application methods and use sites. For agricultural uses, application techniques include tractor-drawn equipment, open and closed mixing/loading, and hand held equipment. Predominant maximum application rates for vegetable crops range from 1 to 2 lb ai/acre; maximum citrus rate is 6 lb ai/acre; maximum rates for tree nuts and fruits is 2 lb ai/acre; outdoor ornamental rates for wettable powders are up to 4 lb ai/acre and up to 0.16 lb ai/gallon for liquid formulations; and up to 8 lb ai/acre for fire ant control in sodfarm turf just prior to harvest. These rates are intended to reflect the upper range of the application rates on the labels, and in some instances the typical or predominant rates. Some of the rates do not necessarily reflect the typical rates actually used in the field (e.g., 5 lb ai/A tobacco rate or 8 lb ai/A sodfarm treatment). Applications of chlorpyrifos include soil incorporated uses, bark treatments, and foliar treatments.

The scenarios were classified as short-term (1-7 days), intermediate-term (1 week to several months) and in some cases long-term (greater than several months) based primarily on frequency of exposure. The occupational handler scenarios for agricultural use are expected to be short-and intermediate term only, while several of the PCO handler scenarios in residential settings (i.e., treatment of homes for insect infestations) were considered to be long-term duration. For the agricultural PCOs, the estimated exposures considered baseline protection (long pants and a long-sleeved shirt, no gloves, and an open cab or tractor), additional personal protective equipment (PPE, which includes a double layer of clothing and gloves and/or a dust/mist respirator), and engineering controls (closed mixing/loading systems for liquids and granulars and enclosed cabs/trucks). For some of the PCO exposure scenarios in residential settings, both baseline and additional PPE were considered. However, because several scenarios were evaluated based on chemical-specific studies submitted by Dow AgroSciences, only the label-recommended clothing was considered (i.e., scenarios with additional PPE or engineering controls could not be evaluated).

4.4.1.1 Occupational Handler Exposure Data Sources and Assumptions

Multiple chemical-specific handler exposure studies were conducted by the registrant and submitted to the Agency. The handler data collected included biological monitoring of urinary 3,5,6-TCP, the primary metabolite of chlorpyrifos, and passive dosimetry data. In the absence of chemical-specific data, PCO potential exposures resulting from handling and applying chlorpyrifos were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 or the Draft Residential SOPs. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. The PHED data used for the mixer/loader for lawn treatment, and granular bait application (hand, belly grinder and push-type spreader) scenarios in residential settings are representative of the chlorpyrifos uses as the surrogate data were monitored for the same uses. In the absence of surrogate data, (e.g., insecticidal dust application) the Draft Residential SOP assumptions were used.

Potential exposures and internal doses were calculated using unit exposures (i.e., normalized to amount of active ingredient handled -- mg/lb ai handled) from both passive dosimetry and biological monitoring data multiplied by the amount of chlorpyrifos handled per day (i.e., lb ai/day). The amount of chlorpyrifos assumed handled per day was derived from the various application rates and the number of acres (or gallons of spray solution) that could be applied in a single day. Dermal and inhalation margins of exposure (MOEs) are presented separately along with a combined total MOE. The total MOE is used to assess the risk.

4.4.1.2 Occupational Handler Risk Characterization

A summary of the short- and intermediate-term risks estimates for PPE and engineering controls is presented in Table 8 for agricultural uses. Table 8 also provides a summary of the range of application rates assessed for chlorpyrifos. Table 9 presents a summary of the short-,

intermediate, and long-term risk estimates for PCOs at non-agricultural use sites, such as residential settings.

MOEs for occupational handlers were derived by dividing appropriate NOAEL, shown on Table 2, by the daily dermal or inhalation exposure estimate. As noted previously, the short-term dermal NOAEL of 5 mg/kg/day is from a dermal rat study, and therefore, no dermal absorption adjustment is necessary. However, both the intermediate- and long-term dermal NOAELs of 0.03 mg/kg/day are based on an oral dog study, and consequently, dermal exposures were adjusted to absorbed dermal doses using an 3% dermal absorption factor. Inhalation exposure estimates were compared directly to the short- and intermediate-term inhalation NOAEL of 0.1 mg/kg/day, and to the long-term NOAEL of 0.03 mg/kg/day based on an oral dog study, assuming inhalation absorption is 100% of oral absorption. For occupationally exposed workers, MOEs >100 (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability) do not exceed HED's level of concern. MOEs below this level would represent a risk concern. A total dermal and inhalation MOE was also calculated because there is a common dermal and inhalation toxicity endpoint (i.e., cholinesterase inhibition).

Agricultural and/or Greenhouse Uses

The results of the intermediate-term handler assessments indicate that none of the potential exposure scenarios provide total dermal and inhalation MOEs greater than or equal to 100 at baseline attire (i.e., long pants, long sleeved shirts, no gloves) and only three of the 16 scenarios at the maximum PPE of coveralls over long pants, long sleeved shirts, and chemical resistant gloves while using open systems. Using engineering controls (i.e., closed systems), only 5 of the 16 scenarios calculated have total MOEs greater than or equal to 100. Even within these acceptable scenarios, not all of the application rates/crops have MOEs greater than or equal to 100. There are insufficient information and data to assess the seed treatment uses, dip applications (e.g., preplant peaches), and dry bulk fertilizer applications to citrus orchard floors. These scenarios are of concern given the results from the other scenarios assessed.

The agricultural handler assessments are believed to be reasonable high end representations of chlorpyrifos uses. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- exposure of an intermediate-term duration (in addition to short-term duration) to assess all uses; and
- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies.

These uncertainties are inherent in most pesticide exposure assessments. The conservative nature of the assessments, however, are believed to be protective of the handlers.

Occupational/Non-Agricultural Uses (e.g., Residential Settings)

The following scenarios result in MOEs that exceed HED's level of concern (i.e., MOE less than 100 for PCOs):

(1) Indoor Crack and Crevice Treatment by a PCO;

(2) Broadcast Turf Treatment by a PCO (long-term applicator, mixer/loader);
(4) Application of Insecticidal Dust Products by a worker;
(5) Application of Granular Baits by a PCO by hand;
(6) Application of Granular Baits by a PCO with a belly grinder;
(7) Application of Granular Baits by a PCO with push-type spreader;
(8) Termiticide Treatments for Pre-Construction by a PCO;
(9) Termiticide Treatments for Post-Construction by a PCO;

The following scenarios result in MOEs greater than 100 that do not exceed HED's level of concern for occupational pesticide handlers in residential settings:

(3) Ready-to-Use Formulated product (Ant Stop) containing 0.5% ai chlorpyrifos, and
(2) Mixer/loader of lawn care products wearing PPE, and working less than several months a year (i.e., intermediate-term duration).

The results of the PCO handler assessment in residential settings for intermediate and/or long-term exposure scenarios indicate that most of the MOEs are less than 100, and therefore exceed HED's level of concern. The only intermediate-term scenarios that result in a MOE consistently above 100 is the use of a 0.5% ready-to-use formulated product (MOE = 140), and lawn care professionals that wear PPE and mix and load lawn products for intermediate durations (i.e., less than several months a year) (total dermal and inhalation MOEs 140-160). The majority of risks were estimated based on chemical-specific biomonitoring studies submitted by Dow AgroSciences (i.e., indoor crack and crevice treatment, broadcast turf application, ready-to-use formulated product, and pre- and post-construction termiticide treatment) in which the PCOs wore label-specified PPE. Several of these studies did not apply the product at the maximum label rate, or only evaluated exposures for a few hours (i.e. 1-3 hours) of the work day, and consequently could underestimate exposures and risks to PCOs. Overall, the exposures and risks for PCOs based on the chemical-specific biomonitoring studies are considered to be central tendency estimates because they evaluated less than a full day's exposure at the maximum label rate or they exclude accidental exposure (e.g., replicate due to a broken hose).

4.4.2 Occupational Postapplication Exposure Scenarios

EPA has determined that there is potential exposure to persons entering treated sites (e.g., scouts and harvesters) after application is complete. Postapplication exposure data were required during the chlorpyrifos Data Call In (DCI) of the reregistration process, since, at that time, one or more toxicological criteria had been triggered for chlorpyrifos.

4.4.2.1 Occupational Postapplication Exposure Data and Assumptions

Multiple chemical-specific postapplication exposure studies were also conducted by the registrant and submitted to the Agency. These studies included biological monitoring and passive dosimetry data, along with dislodgeable foliar residue (DFR) data. Data were collected for citrus, cauliflower, and tomatoes. These data were used in this assessment along with HED default transfer coefficients to assess potential exposures to workers reentering treated sites. Three of the four registrant-submitted DFR studies, in addition to two registrant assessments of their DFR data are included in this assessment. Chemical-specific studies are not available for

all activities and crops that are potentially treated with chlorpyrifos. Therefore, the assessment of postapplication exposures in this document is based on a grouping of activities associated with various representative crops. The potential for dermal contact during postapplication activities (e.g., harvesting) is assessed using a matrix of potential dermal contact rates by activity and associated crops with groupings of "low", "medium", and "high". In addition to this matrix, citrus and tree nuts and fruits are assessed separately.

4.4.2.2 Occupational Postapplication Risk Characterization

The results of the intermediate-term postapplication assessments indicate that restricted entry intervals (REIs) need to be established. The REIs range from 12 days for the "low"crop grouping to 20 days for the "high"crop grouping. REIs for citrus and tree nut and fruit crops are 5 to 6 days for harvesting. A postapplication entry restriction for scouts in citrus and tree nut and fruit crops is 4 days. The timing of the applications are important to note because most of the applications to trees are to the bark during the dormant to early season. Furthermore, long pre-harvest intervals (PHIs) exist for crops such as citrus. Even though there are insufficient information (e.g., timing of applications–dormant/bark versus foliar treatments) and data to assess postapplication activities for ornamental, sodfarm, and soil incorporated uses, these uses are believed to require long REIs (e.g., high application rates and high potential for dermal contact).

The occupational postapplication assessments are believed to be reasonable high end representations of chlorpyrifos uses. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- exposure of an intermediate-term duration (in addition to short-term duration) to assess all uses;
- extrapolating exposure and DFR data by the amount of active ingredient handled or applied;
- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies;
- translating crop-specific DFR data to assess other crops; and
- application timing in comparison to actual potential postapplication exposure scenarios.

These uncertainties are inherent in most pesticide exposure assessments. The conservative nature of the assessments, however, are believed to be protective of the worker.

4.4.3 Residential Handler Exposure

Potential chlorpyrifos residential handler uses include treatment of turf and ornamental plants, as well as indoor use (i.e., for cockroaches, carpenter ants, etc), and structural pest control (i.e., termites). Residential handler exposures to chlorpyrifos can occur via dermal and inhalation routes during handling, mixing, loading and applying activities. As noted previously, in 1997 Dow AgroSciences agreed to work with EPA in limiting household consumer use to only products packaged as ready-to-use in order to minimize exposure to concentrates that require mixing. The exposure duration of these activities was classified as short-term (1-7 days).

4.4.3.1 Residential Handler Exposure Scenarios

EPA has determined that there is potential exposure to residents during application of chlorpyrifos products. Based on residential use patterns, seven major residential exposure scenarios were identified and evaluated for chlorpyrifos:

(1) indoor crack and crevice treatment using an aerosol can;
(2) broadcast turf mixing/loading/application using either a hose end sprayer or a low pressure hand wand;
(3) application of a 0.5% ready-to-use formulated product in a screw top bottle;
(4) application of an insecticidal dust product using a shaker can or bulbous duster;
(5) application of granular bait by hand;
(6) application of granular bait with a belly grinder;
(7) application of granular bait with a push-type spreader;
(8) paintbrush application to wood for an insect infestation; and
(9) treatment of ornamentals (mixing/loading/application) using a low pressure hand wand.

4.4.3.2 Residential Handler Exposure Data Sources and Assumptions

For most cases, residential handler exposure assessments were completed by HED assuming an exposure scenario for residents wearing the following attire: short-sleeved shirt, short pants, shoes and socks, and no gloves or respirator. The only exception is the application of a ready-to-use formulated product, which was evaluated based on a chemical-specific biomonitoring study in which the volunteers wore long pants. PHED values used to estimate daily unit exposure values were obtained from the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 1997). Eight of the nine scenarios were evaluated based on data obtained from PHED.

For broadcast turf application, the area treated per day was assumed to be 0.5 acre for hose end sprayer and 1000 ft^2 for spot treatment using a low pressure hand wand. For application of the granular bait, it was assumed that an average of 0.97 lbs active ingredient was handled, based on the average of 55 replicates from the studies cited in PHED for this use pattern. For a number of scenarios, multiple evaluations were conducted using application rates less than the maximum label rate, or application using different equipment or methods (i.e., ornamental treatment via low pressure hand wand and hose-end sprayer, and granular application via hand, belly grinder and push-type spreader) to assist in risk mitigation and management decisions.

4.4.3.3 Residential Handler Risk Characterization

A summary of the short-term risk estimates, method of evaluation and risk characterization/uncertainties for residential handlers is presented on Table 9. MOEs for residential handlers were derived by dividing appropriate short-term NOAEL, shown on Table 2, by the daily short-term dermal or inhalation exposure estimate. As noted previously, the short-term dermal NOAEL of 5 mg/kg/day is from a dermal rat study, and therefore, no dermal absorption adjustment is necessary. For inhalation, the short-term NOAEL is 0.1 mg/kg/day based on two inhalation studies conducted in rats. For residential applicators, MOEs > 300 (i.e., 10x for interspecies extrapolation, 10x for intraspecies variability and 3x for the FQPA factor) do not exceed HED's level of concern. MOEs below this level would represent a risk concern. A total dermal and inhalation MOE was also calculated because there is a common dermal and inhalation toxicity endpoint (i.e., cholinesterase inhibition).

The results of the residential handler assessment for short- term exposure scenarios indicate that eight of the nine scenarios evaluated have total dermal and inhalation MOEs that exceed HED's level of concern defined by a target MOE of 300. The only short-term scenario that results in a MOE above 300 is scenario (3), the use of a 0.5% ready-to-use formulated product (MOE = 590). The residential handler MOEs ranged from 1 to 897 for dermal risk, from 2.5 to 56,700 for inhalation risk, and from 0.8 to 880 for total dermal and inhalation risk. In some instances, when the product is not applied at the maximum label rate, is maximally diluted and/or is applied using different equipment, the MOEs are above 300. These additional analyses were conducted to assist in risk mitigation and management decisions. The following scenarios result in total MOEs that exceed HED's level of concern for the maximum application rate:

(1) indoor crack and crevice treatment using an aerosol can;
(2) broadcast turf mixing/loading and application using either a hose end sprayer or a low pressure hand wand;
(4) application of an insecticidal dust product using a shaker can or bulbous duster;
(5) application of granular bait by hand;
(6) application of granular bait with a belly grinder;
(7) application of granular bait with a push-type spreader;
(8) paintbrush application to wood for an insect infestation; and
(9) mixing/loading and treatment of ornamentals using a low pressure hand wand.

4.4.4 Residential Postapplication Exposures and Risks

EPA has determined that there are potential postapplication exposures to residents entering treated areas both indoors following residential treatment for cockroaches, termites or other insects and outdoors following lawn treatment or mosquitocide use. In addition, there is a potential for inadvertent oral exposure to children from eating chlorpyrifos-treated soil, grass and/or granules. For residential postapplication activities, the exposure duration is expected to be short-, intermediate- and long-term (1 days to several years) depending on the scenario.

4.4.4.1 Postapplication Exposure Scenarios

HED evaluated the following eight scenarios likely to result in postapplication exposures to residents:

(1) Indoor Crack and Crevice Treatment of kitchen and bathroom;
(2) Indoor Crack and Crevice Treatment of other rooms;
(3) Pet Collar Products;
(4) Termiticide Treatments for Basement, Plenum, Slab and Crawlspace Construction Homes;
(6) Broadcast Lawn Treatment Using a Liquid Spray;
(7) Broadcast Lawn Treatment Using a Granular Formulation;
(8) Aerial and ground-based fogger mosquitocide application; and
(9) Yard and Ornamental Spray Products.

An additional scenario, insecticidal dust product use (scenario 5) was considered, but could not be quantitatively evaluated due to an absence of chemical-specific information and residential SOPs.

HED is in the process of revising the Residential Exposure Assessment SOPs and plans to present some of the major issues to the Science Advisory Panel (SAP) in July 1999. This process may identify specific areas of further concern with respect to chlorpyrifos and exposure to the general population. For example, some of the secondary exposure pathways that EPA is currently addressing and that will be presented to the SAP include exposures resulting from residue tracked into homes from outdoor use, indoor dust, and spray drift. In a recent study, polycyclic aromatic hydrocarbons (PAHs) that are abundant in house dust were shown to increase the toxicity of chlorpyrifos in vitro, particularly at low levels (i.e., 2-50 μM PAHs with 1-180 nM chlorpyrifos-oxon, a metabolite of chlorpyrifos that inhibits acetyl cholinesterase) (Jett et al. 1999). Currently, there are no SOPs available to evaluate these potential exposure pathways. These scenarios however, may be evaluated in the future pending revisions to the residential SOPs.

4.4.4.2 Data Sources and Assumptions for Postapplication Exposure Calculations

HED evaluated four of the eight residential postapplication exposures scenarios based on chemical-specific studies submitted by Dow AgroSciences (i.e., crack and crevice treatment of the kitchen and bathroom (1), broadcast treatment of turf with chlorpyrifos spray (6) and granules (7), and termiticide treatment (4)). Three of these studies (crack and crevice, and lawn studies) included biomonitoring of the urinary metabolite 3,5,6-TCP, in addition to environmental measurements to quantify chlorpyrifos exposures. In the absence of chemical-specific data, the other exposures (scenarios 2, 3 and 8) were evaluated using the equations and assumptions presented in the Draft SOPs for Residential Exposure Assessments guidance document (i.e., indoor crack and crevice treatment of other rooms, and pet collar uses), which are considered to result in high-end exposure estimates. Scientific literature studies, the AgDrift Model and the Draft Residential SOPs were used to evaluate mosquitocide uses.

4.4.4.3 Residential Postapplication Risk Characterization

A summary of the postapplication risk estimates, method of evaluation, and risk characterization/ uncertainties is presented in Table 10. MOEs for residential postapplication exposures were derived by dividing appropriate NOAEL, shown on Table 2, by the daily dermal, inhalation or oral exposure estimate. For residents, the acceptable MOE is 300 (i.e., 10x for interspecies extrapolation, 10x for intraspecies variability and 3x for the FQPA factor). MOEs below this level would represent a risk concern for the Agency. A total dermal and inhalation MOE was also calculated because there is a common dermal and inhalation toxicity endpoint (i.e., cholinesterase inhibition). For child exposures, oral exposure also contributed to the total MOE. The following scenarios result in MOEs less than 300 that exceed HED's level of concern:

(1) Indoor Crack and Crevice Treatment of kitchen and bathroom;
(2) Indoor Crack and Crevice Treatment of other rooms;
(3) Pet Collar Products;
(4) Termiticide Treatments for Basement, Plenum and Slab Construction Homes (some of the MOEs for children exceed HED's level of concern).
(6) Broadcast Turf Treatment Using a Liquid Spray;
(7) Broadcast Turf Treatment Using Granular Formulation;

In addition, by analogy, HED evaluated yard and ornamental spray products (Scenario 9) and

concluded that these products result in comparable doses and short-term MOEs with the lawn care products based on label uses and application rates. Therefore, use of many of these products is likely to result in MOEs that exceed HEDs level of concern.

The following scenarios result in MOEs predominantly greater than 300 that do not exceed HED's level of concern for post-application residential exposures:

(8) Aerial and ground-based fogger mosquitocide application; and
(4) Termiticide treatment (crawl space homes).

In conclusion, seven of the eight scenarios evaluated have MOEs that are less than 300, and therefore exceed HED's level of concern. MOEs for the residential postapplication exposures ranged from 7.5 to 3700 for total risk. The only postapplication scenario that resulted in a MOE consistently above 300 was from the aerial and ground-based fogger mosquitocide applications (MOEs are 2300 and 3600 for children and adults, respectively). The MOEs following termiticide treatment of crawlspace homes were above 300, however, treatment of other construction type homes for termites resulted in MOEs below 300 for children. The exposure and risk estimates based on the chemical-specific studies are considered to be reasonable central-tendency estimates (i.e., arithmetic mean exposure was used to calculate risk). Because three of the chemical-specific studies were conducted in adults, conservative assumptions were used to estimate child exposures. However, because adult activity patterns differ from children, i.e., hand-to-mouth activity, some of the registrant-submitted chemical-specific studies could under-estimate a child's exposure (e.g., lawn studies are not designed to reflect any potential for incidental ingestion of residues from treated turf, soil and/or granules).

An additional scenario, insecticidal dust product use (scenario 5) could not be quantitatively evaluated due to an absence of chemical-specific data or recommended procedures in the Residential SOPs. Nevertheless, HED has concerns about the use of these products based on the very low MOEs (i.e., < 10) calculated using the Residential SOPs for residents or workers that could apply these products. HED recommends that the registrant provide additional information on the potential post-application residential exposures associated with these products.

Table 8
Exposure Variables and MOEs for Agricultural Uses
(Including Non WPS Ornamental Uses) of Chlorpyrifos

Exposure Scenario (Scenario #)	Are Biological Monitoring Data Available? (a)	Application Rates (lb ai/acre) (b)	Daily Acres Treated (c)	Short-Term Total MOEs		Intermediate-Term Total MOEs	
				PPE	Engineering Controls	PPE	Engineering Controls
Mixer/Loader Exposure							
Mixing/Loading Liquids for Aerial/Chemigation Application (1a)	Yes MRID No. 44739302	1.5 predominant max / 4.0 sodfarm White Grub	350	23 / 9	52 / 20	7 / 3	14 / 5

Table 8
Exposure Variables and MOEs for Agricultural Uses
(Including Non WPS Ornamental Uses) of Chlorpyrifos

Exposure Scenario (Scenario #)	Are Biological Monitoring Data Available? (a)	Application Rates (lb ai/acre) (b)	Daily Acres Treated (c)	Short-Term Total MOEs		Intermediate-Term Total MOEs	
				PPE	Engineering Controls	PPE	Engineering Controls
		3.5 citrus (d)	100	34	78	10	21
Mixing/Loading Liquids for Groundboom Application (1b)	Yes MRID No. 42974501	1.5 predominant max / 5.0 tobacco max	80	100 / 30	230 / 69	30 / 9	62 / 19
		8.0 sodfarm fire ants (harvest only)	10	150	340	45	93
Mixing/Loading Liquids for Airblast Application (1c)	Yes MRID No. 43138102	2.0 predominant max such as Fruits & Nuts / 6.0 citrus	40	150 / 50	340 / 110	45 / 15	93 / 31
		4.0 outdoor ornamental bark treatment	10	300	690	90	190
Mixing WP for Aerial/Chemigation Application (2a)	No	2.0 predominant max / 4.0 sodfarm White Grub	350	0.9 / 0.4	23 / 11	0.5 / 0.2	8 / 4
		3.5 citrus (d)	100	1.8	46	0.2	16
Mixing WP for Groundboom Application (2b)	Yes MRID No. 42974501	1.0 predominant max (brassica)	80	8	200	4	72
		4.0 soil treatment ornamentals outdoors / 8.0 sodfarm fire ants (harvest only)	10	16 / 8	400 / 200	8 / 4	140 / 72
Mixing WP for Airblast Application (2c)	No	2.0 predominant max / 6.0 citrus	40	8 / 3	200 / 67	4 / 1	72 / 24
Loading Granulars for Aerial Application (3a)	No	1.95 maximum aerial rate	350	25	270	15	200
Loading Granulars for Ground Application (3b)	Yes MRID No. 44483501 (3b and 8)	1.0 typical corn / 2.0 max corn / 3.0 maximum ground rate (tobacco)	80	210 / 110 / 71	2300 / 1200 / 780	130 / 64 / 43	1700 / 860 / 570
Mixing Dry Flowables for Aerial/Chemigation Application (4a)	No	2.0 predominant max	350	9	NE	2	Not Feasible
		3.5 citrus (no label, assumed same as WP label) (d)	100	18	NE	4	Not Feasible
Mixing Dry Flowables for Groundboom Application (4b)	No	2.0 predominant max (assumed -- no label)	80	40	NE	9	Not Feasible
		4.0 soil treatment ornamentals outdoors (assumed -- no label)	10	20	NE	5	Not Feasible

Table 8
Exposure Variables and MOEs for Agricultural Uses
(Including Non WPS Ornamental Uses) of Chlorpyrifos

Exposure Scenario (Scenario #)	Are Biological Monitoring Data Available? (a)	Application Rates (lb ai/acre) (b)	Daily Acres Treated (c)	Short-Term Total MOEs		Intermediate-Term Total MOEs	
				PPE	Engineering Controls	PPE	Engineering Controls
Mixing Dry Flowables for Airblast Application (4c)	No	2.0 predominant max / 6.0 citrus (no label)	40	80 / 27	NE	18 / 6	Not Feasible
Applicator Exposure							
Aerial (Spray) -- Enclosed Cockpit (5a)	No	2.0 predominant max	350	NE	60	NE	17
		3.5 citrus (d)	100	NE	120	NE	35
Aerial (Granulars) -- Enclosed Cockpit (5b)	No	1.95	350	NE	8	NE	7
Groundboom Tractor (6)	Yes MRID No. 42974501	1.5 predominant max / 5.0 tobacco max / 8.0 sodfarm fire ants	80	NE	310 / 120 / 76	NE	110 / 32 / 20
Airblast Applicator (7)	Yes MRID No. 43138102	2.0 predominant max / 6.0 citrus	40	NE	140 / 35	NE	37 / 12
		4.0 outdoor ornamental bark treatment	10	NE	210	NE	74
Tractor-Drawn Granular Spreader (8)	Yes MRID No. 44483501 (3b and 8)	1.0 typical corn / 2.0 max corn / 3.0 maximum ground rate (tobacco)	80	270 / 140 / 90	330 / 170 / 110	130 / 66 / 44	200 / 100 / 68
Seed Treatment (9)	No	No Data	No Data	No Data	No Data	No Data	No Data
Dip Application (Preplant Peaches) (10)	No	No Data	No Data	No Data	No Data	No Data	No Data
Flagger Exposure							
Spray Applications (11)	No	2.0 predominant max	350	37	880	9	340
		3.5 citrus (d)	100	74	1800	19	690
Granular Applications (12)	No	1.95	350	170	2500	54	1200

Table 8
Exposure Variables and MOEs for Agricultural Uses
(Including Non WPS Ornamental Uses) of Chlorpyrifos

Exposure Scenario (Scenario #)	Are Biological Monitoring Data Available? (a)	Application Rates (lb ai/acre) (b)	Daily Acres Treated (c)	Short-Term Total MOEs		Intermediate-Term Total MOEs	
				PPE	Engineering Controls	PPE	Engineering Controls
Mixer/Loader/Applicator Exposure							
Backpack Sprayer (13)	Yes MRID No. 43027901	0.0417 lb ai/gal *predominant max* / 0.08 lb ai/gal bark beetle treatment / 0.16 lb ai/gal stump treatment	40 gal/day	110 / 58 / 29	NE	25 / 13 / 7	Not Feasible
		3.5 citrus bark	1 A/day	53	NE	12	Not Feasible
		0.039 lb ai/gal / 750 ft2	1000 ft2	3500	Not Feasible	810	Not Feasible
Low Pressure Handwand (14)	Yes MRID No. 43027901	0.0417 predominant max / 0.08 lb ai/gal *bark beetle* treatment / 0.16 lb ai/gal stump treatment	40 gal/day	310 / 160 / 82	NE	98 / 51 / 25	Not Feasible
		3.5 citrus bark	1 A/day	6	NE	2	Not Feasible
		0.039 lb ai/gal / 750 ft2	1000 ft2	10000	Not Feasible	3100	Not Feasible
High Pressure Handwand (greenhouse uses) (15)	Yes MRID No. 43027901	Min. 0.0031 lb ai/gal	1000 gal/day	40	NE	12	Not Feasible
		Max. 0.0063 lb ai/gal		20	NE	6	Not Feasible
		0.039 lb ai/gal / 750 ft2	10000 ft2	1900	Not Feasible	420	Not Feasible
Hydraulic Hand-held Sprayer for Bark / Pine Seedling Treatment (16)	No	3.5 citrus bark	10	28	NE	3	Not Feasible
		0.08 lb ai/gal bark beetle treatment / 0.16 lb ai/ gal pine seedling treatment /	1,000	12 / 6	Not Feasible	3 / 1	Not Feasible
Dry Bulk Fertilizer Impregnation	No	1.0 lb ai / 200 lb fertilizer / acre	unknown	No Data	No Data	No Data	No Data

NE = Not evaluated

(a) Biological monitoring data are available from several chemical-specific studies. Although biological monitoring scenarios are available for some of the scenarios as indicated in this table, passive dosimetry data are presented for comparison because insufficient replicates and/or additional risk mitigation measures were necessary.

(b) Application rates are the maximum labeled rates found on EPA Reg. Nos. 62719-163, -39, -221, -23, -245, -255, -34; -79, -72, -166, -220, 34704-66 (Clean Crop Chlorpyrifos 4E -- sodfarm fire ant rate), 499-367 (499-367 is the only greenhouse label identified; the finished spray solution concentration assumed a density of water for the formulated product), and 10350-22 for animal premise treatments. **"Predominant max"** in this table refers to the most **predominant maximum** application rate found on the labels for the specific formulation and equipment type. Typical rates are also included to characterize the chlorpyrifos uses. Not all application rates are included for all crops, instead, a cross-section of rates are used to represent the uses of chlorpyrifos.

(c) Daily acres treated are based on HED's estimates of acreage (or gallonage) that would be reasonably expected to be treated in a single day for each exposure scenario of concern. The sodfarm fire ant rate is restricted on the label for harvest only, therefore, this rate is limited to the amount of sod that may be harvested in a reasonable time frame. Specific data for harvesting is not available.

(d) The application rates on the Lorsban 4E (EPA Reg. No. 62719-220) and 50W (EPA Reg. No. 62719-39) labels indicate that for citrus at the 6.0 lb ai/A rate it is necessary to use 100 to 2,400 gallons per acre dilute spray. Therefore, this rate is not expected to be feasible for an aerial applicator. The label language should be clarified so that the 6.0 lb ai/A rate is for ground only. Additionally, citrus orchards are believed to be relatively small plots and 100 acres per day is assumed in the assessment for aerial applications.

Table 9. *Estimates of Exposures and Risks to Commercial Applicators and Residents* Applying Chlorpyrifos in the Residential Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
(1) Indoor Crack & Crevice Treatment						
Long term PCO	double layer clothes, chemically-resistant boots and gloves, eye protection	Biomonitoring study *MRID No. 44444801* (minimum, mean and maximum amount handled)	17-5900	58 -2000	13 -4500	Central-tendency risk estimates for maximum and minimum amounts handled, respectively; MOEs less than 100 for workers that could handle ≥0.02 lb ai/day (the mean amount handled in the study). Only two of 15 replicates reflect the maximum label concentration of 0.5% ai. (avg of 0.29% ai was handled in study)
Short-term Residential Applicator	SS, SP, no gloves	Residential SOPs (PHED V1.1)	159	292	100	High-end risk estimates; assumes application of one 16 oz. aerosol can containing 1% ai
(2) Broadcast Turf Application (Intermediate and Long-Term for PCOs; Short-Term for Residential Applicators)						
Applicator	single layer clothes, chemically-resistant knee high boots and gloves, hat (knee high boots not required by label)	Biomonitoring Study MRID No. 44729401 (20% of label maximum rate or adjustment for label-recommended max application rate)	Biomonitoring: 75 (IT&LT)			Central-tendency risk estimates; product applied at 20% of label maximum; study evaluated a 6 hour work day
			Label Max: 15 (IT&LT)			High-end risk estimates; product applied at label maximum
Mixer/Loader (liquid)	Baseline	PHED V1.1 (biomonitoring study rate and 20% or maximum label rate)	1.6 -8.1	120-600	2 - 8 (IT&LT)	Central-tendency to High-end risk estimates; maximum ai handled in study with maximum and 20% of label rate, respectively
	single layer clothes, gloves		206 -1032	400-1980 (IT) 120 -600 (LT)	140-680 (IT) 75- 380 (LT)	
	double layer clothes, gloves		280 -1400		160-820 (IT) 83 -420 (LT)	
Residential Mixer/Loader/ Applicator Broadcast with Hose End Sprayer	SS, SP, no gloves	Residential SOPs (PHED V1.1) (min and max dilution rates)	6-23	368-1470	6-23	Central-tendency to High-end risk estimates; Low confidence in exposure estimates from PHED V1.1

Table 9. Estimates of Exposures and Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential Environment						
Application Scenario	**Clothing**	**Method of Evaluation**	**MOE**			**Risk Characterization/ Uncertainties**
			Dermal	**Inhalation**	**Total**	
Residential Mixer/Loader/ Applicator Spot treatment with Low Pressure Handwand	SS, SP, no gloves	Residential SOPs	37	2490	37	Central-tendency to High-end risk estimates; Low confidence in dermal exposure estimates, and medium confidence in inhalation exposure estimates
(3) Ready-to-Use 0.5% a.i. Formulated Product						
Intermediate-term PCO Baseline	SS, LP, no gloves	Biomonitoring Study MRID No. 44739301	143	3,448	140	Central-tendency risk estimates; based on 1 hour exposure, but less clothing than a typical PCO would wear.
Short-term Residential Applicator	SS, LP, no gloves	Biomonitoring Study MRID No. 44739301	714	3,448	590	Central-tendency to high-end risk estimate; assumes resident applies five 24 oz bottles of product/day, however, homeowner wore long pants and current HED policy is to evaluate exposures for short pants.
(4) Insecticidal Dust Product (Shaker Can or Bulbous Duster)						
Residential Applicator (1% ai chlorpyrifos; 2.83 g ai)						
Short- term	NA	Residential SOPs	1.2	2.5	0.8	High-end risk estimates; assumes an individual is exposed to 10% of the ai in the dust product.
Worker (7% ai chlorpyrifos; 7.91 g ai)						
Short- and intermediate term	NA	Residential SOPs	0.1 -0.4	7.5	0.09 - 0.42	High-end intermediate and short-term risk estimates, respectively; assumes an individual is exposed to 10% of the ai in the dust product.
Kurtz and Bode (1985) 5% ai; 9.5-11 g ai (short-term 15 minute application)						
Residential Applicator	SS, LP, no gloves	Scientific Literature Study	71		71	High-end risk estimates; resident may apply 3-4 times less ai than evaluated
PCO	LS, LP, gloves	Scientific Literature Study	78		78	Central-tendency risk estimates; PCO may apply product for more than 15 minutes a day

Table 9. Estimates of Exposures and Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential Environment						
Application Scenario	**Clothing**	**Method of Evaluation**	**MOE**			**Risk Characterization/ Uncertainties**
			Dermal	**Inhalation**	**Total**	
(5) Granular Bait (Hand Application)						
PCO (intermediate-term)	LS, LP, gloves	PHED V1.1	1	15	1	High-end risk estimates; medium confidence in PHED unit exposure estimates which are based on a single study in which a test subject wearing chemical-resistant gloves spread the granular bait around the outside of the residence and. over 90 percent of the samples contained no detectable material.
Residential Applicator (short-term)	SS, SP, no gloves	Residential SOPs	1	15	0.8	
(6) Granular Bait (Belly Grinder)						
PCO (intermediate-term)	LS, LP, gloves	PHED V1.1	8	120	7	High-end risk estimates; low and high confidence in the dermal and inhalation exposure estimates, respectively
Residential Applicator (short-term)	SS, SP, no gloves	Residential SOPs	3	120	3	
(7) Granular Bait (Push-type Spreader)						
PCO (intermediate-term)	LS, LP, gloves	PHED V1.1	57	1150	54	High-end risk estimates; low and high confidence in the dermal and inhalation exposure estimates, respectively
Residential Applicator (short-term)	SS, SP, no gloves	Residential SOPs	120	1150	110	

Table 9. Estimates of Exposures and Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential Environment						
Application Scenario	**Clothing**	**Method of Evaluation**	**MOE**			**Risk Characterization/ Uncertainties**
			Dermal	**Inhalation**	**Total**	
Termiticide Treatments						
(8) Pre-Construction (1.44% chlorpyrifos as Dursban TC) (long-term)						
Mixer/Loader/ Applicator (3 hour average exposure)	label-specified PPE: single layer clothes and forearm-length chemically-resistant gloves (forearm length gloves not required by label)	Dosimetry and air monitoring from Registrant Study MRID No. 44589001	19	67	15	Low-end risk estimates for workers that wore double layer of clothing and forearm length gloves not required by the label; Central-tendency risk estimates for workers that wore a single layer of clothing and forearm length gloves; assumes 3 hour exposure, which could underestimate risks to workers exposed > 3 hrs/day
	double layer clothes (LS,LP, coveralls, rubber boots, and forearm-length gloves) (coveralls and forearm-length gloves not required by label)		63	67	33	
Tarp puller	with forearm-length gloves (LS,LP, leather and/or rubber boots and hat)	Dosimetry and air monitoring from Registrant Study (1-8 tarps) MRID No. 44589001	169-1322	179-1430	87-690	Central-tendency risk estimates; assumes workers pull 1-8 tarps/day (7 min/tarp), could underestimate risks to workers who pull > 8 tarps/day (i.e., >1 hr exposure/day). All total MOEs < 100 for 8 tarp/day. Also, workers wore forearm length gloves not required by the label which reduce estimated exposure.
	without gloves (LS,LP, leather and/or rubber boots and hat)		47-373	245-1961	39-310	
(9) Post-Construction (1% chlorpyrifos as Dursban TC) (long-term)						
Mixer/Loader/ Applicator	Label-specified PPE: LS, LP, chemically resistant gloves, hat, eye protection and half face piece respirator in confined spaces; During M/L: 2 layers clothes and chemically-resistant shoes (not label-required)	Biomonitoring: 4.3 MRID No. 44729402 (n=5)	7		7	Central-tendency risk estimate
		Dosimetry and air monitoring MRID No. 44729402 (n=14)	12	33	9	Central-tendency risk estimate; excludes worker with higher exposure (10X greater than mean) due to a broken hose

Table 9. Estimates of Exposures and Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential Environment						
Application Scenario	**Clothing**	**Method of Evaluation**	**MOE**			**Risk Characterization/ Uncertainties**
			Dermal	**Inhalation**	**Total**	
(10) Paint Brush (Short-term)						
Residential Applicator	SS, SP, no gloves	Residential SOPs	37	590	35	Central-tendency risk estimates; low to medium confidence in dermal exposure estimates and medium confidence in inhalation exposure estimates; Assumes resident applies 1 gallon of diluted product in a day
(11) Ornamental Application (Short-term)						
Residential Mixer/Loader/ Applicator Low pressure Handwand	SS, SP, no gloves	Residential SOPs (minimum : 1 oz/3gal H20)	269	17950	270	Central-tendency to high-end risk estimates; low and medium confidence in the dermal and inhalation exposure estimates, respectively. Assumes resident applies 5 gallons of diluted product/day.
		Residential SOPs (typical 4 oz/3 gal H20)	70	4670	69	
		Residential SOPs (max. 1 qt/3 gal H2O)	8	561	8	
Residential Mixer/Loader/ Applicator Hose End Sprayer	SS, SP, no gloves	Residential SOPs (minimum : 1 oz/3gal H20)	897	56700	880	Central-tendency to high-end risk estimates; low confidence in the dermal and inhalation exposure estimates. Assumes resident applies 5 gallons of diluted product/day.
		Residential SOPs (typical 4 oz/3 gal H20)	233	14700	230	
		Residential SOPs (max. 1 qt/3 gal H2O)	28	1770	28	

LS=Long sleeves; LP = Long pants; SS = short sleeves; SP = short pants
H20 = water; IT = intermediate term; LT = long term

Table 10. Estimates of Post-Application Exposures and Risks to Residents				
Reentry Scenario	Method of Evaluation	Average MOE		Risk Characterization/ Uncertainties
		Adult	Child	
(1) Crack & Crevice Treatment of Kitchen and Bathroom (Short and Intermediate Term)				
Maximum 1-Day Inhalation Exposure:	Biomonitoring Study, with environmental measurements	560	130	Central-tendency to High-end risk estimates; assumes exposure exclusively through inhalation and that children spend 21 hours/day exclusively in the room with highest air concentration.
10-Day TWA Inhalation Exposure		670	360	Central-tendency to High-end risk estimates, assumes exposure exclusively through inhalation
(2) Crack & Crevice Treatment Using Residential SOPs (Short-term)				
Dermal Exposure From Carpets	Highest deposition from family room in biomonitoring study (room adjacent to treatment) and Residential SOPs	88	94	High-end risk estimates; highest deposition from room adjacent to treatment in biomonitoring study was used in conjunction with conservative exposure assumptions.
Dermal Exposure From Surfaces		177	187	
Oral Exposure		NE	299	
(3) Pet Collar Uses (11 month efficiency) (Long-term)				
Dog: Collar (EPA No. 45087-49; 3.44 g ai)				
Dermal	Residential SOPs	670 - 1300	140 -290	High-end total risk estimates; assume daily contact with collar, and that 1% ai is available from collar over 11 months equally from dermal and inhalation exposure routes. (MOEs 290-1300 if assume exposure is exclusively through dermal exposure).
Inhalation		40	9	
Total Exposure (50:50 dermal & inhalation exposure)		39	8	
Cat Collar (EPA No. 4306-16; 0.93 g chlorpyrifos)				
Dermal	Residential SOPs	2500 - 5000	530 -1100	High-end total risk estimates; assume daily contact with collar, and that 1% ai is available from collar over 11 months equally from dermal and inhalation exposure routes. (MOEs >300 if assume exposure is exclusively through dermal exposure).
Inhalation		150	32	
Total Exposure (50:50 dermal & inhalation exposure)		150	31	
(4) Termiticide Treatment (Short, Intermediate and Long-term)				

Table 10. Estimates of Post-Application Exposures and Risks to Residents				
Reentry Scenario	**Method of Evaluation**	**Average MOE**		**Risk Characterization/ Uncertainties**
		Adult	**Child**	
Crawlspace	Registrant-submitted study *with environmental* measurements for 1 year post treatment (MRID No. 40094001)	1400-2600	410-770	High-end risk estimates based on mean value of *maximum detected concentration from 8 homes* of similar construction and conservative exposure assumptions. (MOEs <300 only for children exposed to air measurements in basement homes on days 1-30 and at 1 year, in plenum homes on days 1-30 and slab homes on day 1).
Basement		500-1600	150-500	
Plenum		420-2900	130-910	
Slab		770-3700	240-1100	
(5) Insecticidal Dust Products (Insufficient data to evaluate; see text)				
Broadcast Turf Application (Short-term)				
(6) 0.29 Percent Chlorpyrifos Spray				
Inhalation	*Biomonitoring Study, with* environmental measurements	*170*	*20*	*Central-tendency risk estimates based on arithmetic* mean exposure from biomonitoring study in adults; study does not address frequent hand to mouth activity of children, or incidental ingestion of soil or residues on treated grass by children.
Dermal		10	12	
Oral		NE	400	
Total Absorbed Dose		*9*	*7.5*	
(7) Granular Formulation of 0.5% Chlorpyrifos				
Inhalation	Biomonitoring Study, with environmental measurements	330	400	Central-tendency risk estimates based on arithmetic mean exposure from biomonitoring study in adults; does not adequately address frequent hand to mouth activity of children, or incidental ingestion of soil or granules by children
Dermal		190	90	
Oral		NE	6000	
Total Absorbed Dose		120	73	

Table 10. Estimates of Post-Application Exposures and Risks to Residents				
Reentry Scenario	**Method of Evaluation**	**Average MOE**		**Risk Characterization/ Uncertainties**
		Adult	**Child**	
(8) Aerial and Ground-Based Fogger Mosquitocide Application (Short-term)				
Dermal	Literature studies, the AgDrift Model and the Residential SOPs	3600	3800	High-end risk estimates based on the Residential SOPs
Oral (hand to mouth)		NE	6100	
Oral (Turfgrass Ingestion)		NE	54000	
Oral (Soil Ingestion)		NE	2000000	
Total Exposure		3600	2300	
(9) Yard and Ornamental Sprays (Evaluated based on analogy to Lawn Products; see text)				

NE = not evaluated.

4.4.4.4 Incident Reports

Chlorpyrifos is one of the most widely used insecticides in the home both by consumers and PCOs or exterminators. In a 1990 EPA-sponsored survey of pesticide use in households, chlorpyrifos was the fourth most commonly used insecticide, present in 18% of all households. A 1993 EPA survey of PCOs found it was the number one insecticide in use and accounted for a quarter of the poundage used in residential settings. Consequently, there have been many reports of human exposure and poisonings due to the widespread use of chlorpyrifos. The human poisoning incidents associated with chlorpyrifos exposure have been evaluated and summarized in the attached memorandum from J. Blondell to D. Smegal, June 30, 1999.

Data from the Nation's Poison Control Centers in 1996 reported approximately 116,000 unintentional exposures to all pesticides, of which, 16% were due to organophosphate (OP) pesticides, and 5,188 or 4.5% were attributed to chlorpyrifos. Given that 30% of the organophosphate poisonings were not specifically identified by active ingredient, the actual number of chlorpyrifos cases is probably close to 7,000 or 6% of all pesticide-related exposures. Many of these exposures involve small children who were exposed but never developed symptoms. In 1996 there were 1,109 symptomatic cases related to chlorpyrifos that were judged to have effects related to the exposure, although most (83%) had only minor symptoms (e.g., headache, nausea, vomiting, dizziness and diarrhea) that could be treated at home. From 1993 through 1996, there were an average of 116 unintentional chlorpyrifos cases per year with moderate to severe outcomes (including one fatality) reported in residential settings.

The risk from chlorpyrifos exposures is very similar to the other OP pesticides (e.g., diazinon, malathion, dichlorvos) that have significant residential uses for both children and adults. The one exception is the percent of cases with fatal or life-threatening outcome (not including suicide attempts), where chlorpyrifos had the highest percentage (0.456%) of any of the other 13 OP pesticides, that was 50% higher than any of the non-OP pesticides. Between 1993 and 1996, there was one fatality and 34 life-threatening cases attributed to chlorpyrifos exposure. The fatality was a 22 month old boy who accidently ingested chlorpyrifos that had been placed in a cup. Measures called for in the 1997 Chlorpyrifos Risk Reduction Plan, in part, are aimed a preventing such poisoning incidents.

Chlorpyrifos ranked third of the 13 OPs for serious outcomes resulting from exposure to environmental residues left after application or use. Environmental residues accounted for 15% of the chlorpyrifos exposures and 30% of the cases with serious outcomes (moderate or life-threatening), which was double the incidence for non-OP pesticides.

A particular concern with chlorpyrifos are reports of exposures and poisonings related to use by PCOs. A review of the Poison Control Center data for four years (1993-1996) found over 1000 reports of exposure (250 per year) to chlorpyrifos products that would most commonly be used by PCOs in residential settings. A total of 325 of these cases were symptomatic, 241 cases were seen in a health care facility, 35 were hospitalized and 16 were admitted to an intensive care unit (ICU). Chlorpyrifos PCO products accounted for 9% of the exposures, but 21-24% of the life-threatening/fata cases, hospitalized cases and cases seen in an ICU. Note that the number of cases involving PCO products is relatively small compared to the exposure and symptomatic cases involving consumer products. Just 4% of the product-identified chlorpyrifos exposures in children under age six involved PCO products, and for adults and children over age six the figure was 15%. Also, some of the more serious cases, both for PCO and homeowner products, were

due to broadcast carpet treatment, fogger and pet uses that were voluntarily canceled in 1997.

Another source of concern with all the OP pesticides, including chlorpyrifos, are the frequent anecdotal reports of chronic neurobehavioral effects and multiple chemical sensitivity. Neurobehavioral effects reported include persistent headaches, blurred vision, muscle weakness, and problems with mental function including memory, concentration, depression, and irritability. Such effects have been reported in a small proportion of the acute symptomatic cases. HED suspects that these effects are caused by the acute poisoning, partly from a case-control study in California and partly from case-control (cross sectional) studies of other OP pesticides similar to chlorpyrifos. However, there is limited evidence that acute chlorpyrifos poisoning causes chronic adverse health effects. Among the symptomatic chlorpyrifos cases reported to Poison Control Centers, 3% reported effects lasting longer than a week (ranked first, and twice the incidence of non-OPs), and 1% reported effects lasting more than a month (ranked second, and three times the incidence of non-OPs) than most other pesticides. This finding is consistent with an earlier review that suggested chlorpyrifos may be a cause of chronic neurobehavioral effects in some subsets of sensitive people who have been poisoned (Blondell and Dobozy 1997). As a result of these concerns, Dow AgroSciences has agreed to undertake an epidemiologic study of manufacturing workers. With EPA support, NIOSH is undertaking a study of about 200 PCOs that apply chlorpyrifos in North Carolina. An extensive battery of neurological and neurobehavioral tests have been administered and a report of the results is due in 1999.

As noted previously, four uses of chlorpyrifos have been voluntarily canceled and removed from the market: paint additives; shampoos, sprays and dips used on pets; indoor broadcast flea control products; and household foggers. All of these residential uses involve either concentrates or widespread applications that involve greater potential for exposure to consumers than do other forms and uses of chlorpyrifos. Therefore, substantially less exposures and hazards are expected when additional years of poisoning surveillance data become available. Dow AgroSciences is continuing its' efforts to monitor poisoning incidents through its agreement with a Poison Control Center that takes telephone contacts from the public and the health care community concerning chlorpyrifos. Follow up information to determine the circumstances that lead to exposure and poisoning should be useful.

4.4.5 Pet Incident Reports

A review and analysis of the poisoning incident reports on domestic animals for chlorpyrifos was conducted in 1995 (attached memo from V. Dobozy to B. Kitchens, January 23, 1995) and was updated in 1999 (attached memo from V. Dobozy to D. Smegal, April 26, 1999, D255514). In the 1995 analysis, poisoning incidents in dogs and cats were categorized as exposure by direct applications (flea and tick dips, sprays, collars, etc) or by premise applications (household and lawn treatments). The analysis found that the majority of the incidents in domestic animals involved cats, although the chemical is registered only for use in flea collars for this species. Cats that were exposed to products registered only for use on dogs, mainly dips, experienced a high incidence of death (30%). There was also evidence of misuse of treatment products, including practices such as applying these products directly to animals and not removing pets from premises during applications.

In 1996, PR Notice 96-6 was finalized, which requires the revision of labels for all products administered directly to animals to ensure adequate directions for use and warning information.

In 1997, the registrant voluntarily agreed to cancel chlorpyrifos registrations for indoor broadcast flea control and direct application pet products (sprays, shampoos, and dips), except flea collars, to establish specific protection measures for pets during and immediately after application, and to expedite implementation of PR Notice 96-6 on pet products.

An evaluation of incident reports for domestic animals for the years 1996 through 1998 (memo from V. Dobozy to D. Smegal, April 26, 1999, D255514) revealed that there has been a decrease in the percentage of incidents resulting from exposure to products registered for direct use on animals, but an increase in the percentage of incidents resulting from premise exposure. In addition, deaths are still being reported, especially for cats. The cancellation of indoor broadcast flea control applications and products for direct application to dogs and cats should reduce the risk of serious adverse reactions and deaths, however time is required to eliminate all chlorpyrifos products from store shelves. Therefore, it may be premature to review the Incident Data System (IDS) for evidence that these actions were effective.

4.4.6 Cumulative Exposure

Chlorpyrifos is a member of the organophosphate class of pesticides. All pesticides of this class contain phosphorus and other members of this class of pesticides are numerous and include azinphos methyl, diazinon, dichlorvos, dicrotophos, dimethoate, disulfoton, methamidophos, methidathion, monocrotophos, oxydemeton methyl, phorate, phosmet, and pirimiphos-methyl to name a few.

In considering whether to establish or reassess tolerances, EPA is required to consider available information concerning the cumulative effects of a particular pesticide's residues and other substances that have a common mechanism of toxicity. Chlorpyrifos is an organophosphate pesticide. EPA considers organophosphates to express toxicity through a common biochemical interaction with cholinesterase which may lead to a myriad of cholinergic effects and, consequently the organophosphate pesticides should be considered as a group when performing cumulative risk assessments. EPA is currently developing methods to conduct cumulative assessments. When these methods are completed and peer reviewed, EPA will proceed with a cumulative assessment of the organophosphates. The current assessments address only the risks posed by chlorpyrifos.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATION

An aggregate risk estimate was not conducted for any duration (i.e., acute, chronic, short- or intermediate-term) because some of the acute and chronic dietary exposures, and the total residential MOEs (dermal, inhalation, and inadvertent oral exposures) for all the residential post-application exposure scenarios, except mosquitocide use, alone exceed HED's level of concern. HED recommends that the Agency explore possible mitigation measures to reduce the potential for dermal, inhalation, and inadvertent oral exposure to chlorpyrifos in residential settings and in the diets of children.

Dow AgroSciences has submitted a probabilistic Integrated Exposure Assessment (MRID No. 44104001, September 1996). This submission is in internal HED review, because the Agency policy on aggregate probabilistic risk assessment is still in development. This submission,

however, has been used by the Agency in developing policy and will be evaluated once this policy is finalized and has undergone peer review.

6.0 CONFIRMATORY DATA

Additional data requirements have been identified in the attached Science Chapters and are summarized here.

Toxicology Data for OPPTS Guideline:

HED has recommended and the registrant has developed a protocol for a Repeated Exposure Neurotoxicity Study of Sensory Electrophysiology. This study will also include measurement of neurotoxic esterase (NTE). It is expected that this would be a 28 day 2 dose, oral exposure study. In addition to the neurophysiological and neurochemical measures, neuropathological assessment focused on central/peripheral axonopathic changes associated with OPIDN (organophosphate-induced delayed neuropathy should also be performed). This is special study for which no single EPA guideline provides complete guidance. EPA has a guideline for 28 day hen studies of organophosphates that may cause OPIDN that includes guidance for neuropathology and NTE measurements (US EPA 1998; 870.6100). EPA has a guideline for examining peripheral nerve function (US EPA 85-SS1998; 870.6850) and a guideline for sensory evoked potentials (US EPA 1998; 870.6855). The current protocol for this special study has been developed by the registrant working voluntarily in conjunction with EPA. While EPA has not required this study, EPA maintains the right to require further study, based on concerns for potential health effects, consistent with its obligations under FIFRA. This study is currently underway, with an anticipated completion date of June 1999.

Product and Residue Chemistry Data for OPPTS Guidelines

Product Chemistry. Forty (40) MP's have been identified. Guideline 830.6314 data requirements remain outstanding for the DowElanco 99% T. Data remain outstanding for all other chlorpyrifos MPs; for many MPs no product chemistry data have been submitted. The reregistration guidelines for product chemistry data requirements are complete, provided that the registrants submit the data required in the attached summary tables for the chlorpyrifos MPs, and either certify that the suppliers of starting materials and the manufacturing processes for the chlorpyrifos technicals and manufacturing-use products have not changed since the last comprehensive product chemistry review or submit complete updated product chemistry data packages.

Residue Chemistry. The following confirmatory data requirements and/or label revisions for magnitude of the residue in plants (Guideline 860.1500) remain outstanding or are now required:

- For asparagus, no additional residue data are required. However, a label revision is needed. The maximum equivalent rate of 1.9 lb ai/A specified by a homeowner-use label (EPA Reg. No. 62719-56) should be adjusted to reflect the maximum registered rate of 1.0 lb ai/A for which adequate residue data are available. In a letter to the Agency dated 5/8/95 the registrant committed to correcting the label directions to 1.0 lb ai/A at the next label printing.

- For corn, label restrictions prohibiting feeding of silage, forage, or fodder to meat or dairy animals are not practical and must be removed from SLN DE930004 and FL940003 labels. Additional data must be submitted to determine if established tolerances on corn forage and fodder are adequate for these uses. Alternatively, these SLN uses may be canceled.

- For cotton, feeding restrictions for gin trash (gin by-products) are not practical and must be removed from product labels. Appropriate tolerances for cotton gin by-products must be proposed. The proposal must be supported by adequate residue data conducted according to the maximum use patterns.

- For crops grown solely for seed (clover, and grasses), tolerance proposals and adequate field residue data are required to support SLN (Section 24-c) uses. The Oregon Clover Association has indicated that it will support chlorpyrifos SLN (OR850032) use on clover grown for seed. The requirements specified in the Addendum to the Chlorpyrifos SRR remain outstanding. For grasses grown for seed, appropriate tolerances for residues of chlorpyrifos *per se* in/on grass forage and hay must be proposed. The proposal must be supported by adequate residue data conducted according to the maximum use patterns specified by NV940002, and OR94032. Alternatively, these SLN uses may be canceled.

- For mint, Table 1 (OPPTS Test Guidelines 860, August 1996) requires data for peppermint and spearmint tops (leaves and stems). Mint hay is no longer considered a RAC. Additional data are required for peppermint and spearmint tops (leaves and stems).

- For peppers, the requirements specified by the Addendum to the Chlorpyrifos SRR to submit English translations of labels for all products that permit use of chlorpyrifos on peppers imported to the U.S. have not been fulfilled. Chlorpyrifos use on peppers was approved at the issuance of the SRR, SLN (FL920007, FL920009, GA930003, and GA930004).

- For sorghum, data are required for aspirated grain fractions.

- For tomatoes, the requirements specified by the Addendum to the Chlorpyrifos SRR to submit English translations of labels for all products that permit use of chlorpyrifos on tomatoes imported to the U.S. have not been fulfilled. These data requirements remain outstanding. Chlorpyrifos use on tomatoes was approved at the issuance of the SRR, SLN (FL920010, GA930003, and GA930004).

- For the tree nuts group (almonds, filberts, pecans, and walnuts), the Addendum to the Chlorpyrifos SRR did not require additional data to support the established crop group tolerance. However, an examination of the recently amended labels for the 4 lb/gal EC formulation (EPA Reg. Nos. 62719-23 and 62719-220) indicated that a maximum seasonal rate of 10 lb ai/A was inadvertently approved for pecans. The available residue data, reflecting combined residues of chlorpyrifos and TCP in/on pecans and other representative members of this crop group, only support a maximum seasonal rate of 5 lb ai/A. If the registrant wishes

to support a seasonal rate of 10 lb ai/A, then additional data are required. Alternatively, the labels for pecans may be revised to reflect a maximum seasonal rate of 5 lb ai/A. In a letter to the Agency dated 5/8/95, DowElanco stated that they would modify labels to reflect a maximal seasonal use rate of 5 lb ai/A for pecans at the next label printing. The latest approved label for Lorsban 4E (EPA Reg. No. 62719-220), dated 4/8/96 did not include this modification. The labels should be revised or appropriate residue data supplied.

- For wheat, data are required for aspirated grain fractions.

[Note: The field trial data submitted for asparagus, apples, sugar beets, and tree nuts depict combined residues of chlorpyrifos and TCP. In the absence of adequate data depicting chlorpyrifos *per se* on the commodities of these crops, the established tolerances, for tolerance reassessment purposes, should remain at the existing levels. It is the registrant's prerogative to petition the Agency and submit additional field residue data depicting chlorpyrifos *per se* in/on these crops if tolerance-level reductions or lower anticipated residue calculations are desired.]

GLN 860.1520: Magnitude of the Residue in Processed Food/Feed

According to Table 1 (August 1996) OPPTS 860.1000 Test Guidelines residue data for sorghum flour are not needed at this time because it is used exclusively as a component of drywall, and not as a food or animal feed item, in the US. However, because 50% of the worldwide sorghum production is used for human consumption, data may be needed at a later time.

The requirements for processing data on alfalfa meal are waived because residue data indicate that levels of chlorpyrifos *per se* are not likely to exceed the established tolerance in alfalfa hay following tests conducted according to registered uses. In addition, no sweet corn processing data are required since adequate corn forage data are available.

The available processing data for apples and sugar beets depict combined residues of chlorpyrifos and TCP. In the absence of adequate data depicting chlorpyrifos *per se* on the processed commodities of these crops, the established feed additive tolerances, for tolerance reassessment purposes, should remain at the existing levels. It is the registrant's prerogative to petition the Agency and submit additional processing data depicting chlorpyrifos *per se* in/on these commodities if tolerance-level reductions or lower anticipated residue calculations are desired.

GLNs 860.1850 and 860.1900: Confined/Field Rotational Crops

Provided that Dow AgroSciences modifies all labels for its chlorpyrifos containing products to limit application to 5 lb ai/A/season on those crops where rotation to another crop could occur (as was stated in their letter to the Agency dated 8/12/94), HED will not require field rotational crop studies. Furthermore, a 30 day plant back interval for rotational crops would then be appropriate.

Occupational Exposure Data for OPPTS Guidelines

HED has insufficient data for the following scenarios:

- seed treatment uses
- dip applications (e.g., preplant peaches)
- dry bulk fertilizer applications to citrus orchard floors

These scenarios are of concern given the results from the other scenarios assessed. In addition, there is insufficient information and data to assess the post-application activities for ornamental, sodfarm, and soil-incorporated uses. However, HED defers data requirements until risk management decisions have been finalized.

In addition, HED could not evaluate the postapplication exposures and risks associated with use of insecticidal dust products due to an absence of chemical-specific data or recommended procedures in the Residential SOPs. Nevertheless, HED has concerns about the use of these products based on the very low MOEs (i.e., < 10) calculated using the Residential SOPs for residents or workers that could apply these products. HED recommends that the registrant provide additional information on the potential post-application residential exposures associated with these products.

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