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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: **April 20, 2000**

SUBJECT: **Chlorpyrifos incident review update, DP Barcode 263894, Chem. No. 059101 HED Review of MRID nos. 43480001, 44039901, 44186301, 44245801, 1997 Epidemiology Panel Report, and 1995 critique of EPA's review of neuropathy allegations**

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Background

This memorandum supercedes previous versions of the "Chlorpyrifos Incident Review Update" (DP Barcode 254977 and 259617) by Jerome Blondell, dated April 16, 1999, June 30, 1999, and September 27, 1999. The revision reflects comments and additional data received during and since the public comment period, Oct. 27 through Dec. 27, 1999 (Federal Register 64(207):57876-7), on the EPA preliminary risk assessment for chlorpyrifos.

This review provides summary and update of the memorandum, Review of Chlorpyrifos Poisoning Data, by Jerome Blondell, Ph.D., M.P.H. and Virginia A. Dobozy, V.M.D., M.P.H. to Linda Propst, Reregistration Branch, Special Review and Reregistration Division, dated January 14, 1997. Six evaluations of human data submitted by DowElanco/Dow AgroSciences were also considered in the preparation of this review. These evaluations covered chlorpyrifos incident data, allegations of neuropathy, morbidity experience in manufacturing employees, allegations of teratogenicity, assessment of the Blondell and Dobozy review, and an Epidemiology Blue Ribbon Panel Report. A separate memorandum reviewing these evaluations was prepared by

Jerome Blondell, Health Effects Division (HED) and sent to Mark Hartman, Review Manager, Special Review and Reregistration Division dated February 3, 1999 (see attachment).

Summary

As a result of the widespread use of chlorpyrifos, there have been numerous exposures and poisonings. The majority of poisonings result in minor, transitory effects. Detailed analysis of the poisoning data has been used to identify specific use patterns that are more likely to be associated with pesticide poisoning. In addition to acute poisoning, chlorpyrifos has been reported to be associated with chronic effects in humans, including chronic neurobehavioral effects, peripheral neuropathy, and multiple chemical sensitivity. Neurobehavioral effects reported include persistent headaches, blurred vision, unusual fatigue or 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. The Agency suspects that these effects are caused by acute poisoning based on case-control studies in California and North Carolina of chlorpyrifos as well as studies of other organophosphate pesticides similar to chlorpyrifos.

The main source of serious, acute incidents of chlorpyrifos poisoning had been liquids (not including aerosol cans) used by homeowners or Pest Control Operators (PCOs) indoors or outdoors, termite treatments, and liquid sprays and dips applied to domestic animals. However, in 1998 the uses of sprays and shampoos on pets, broadcast uses on carpets, paint additives, and indoor fogger use, which accounted for 20-25% of exposures and symptomatic cases reported to Poison Control Centers, were voluntarily canceled. However, even when these canceled uses are excluded, it appears that poisonings (usually due to misuse) are likely to be more serious when applied by a PCO . This is supported by reports received by the American Association of Poison Control Centers, the California Pesticide Illness Surveillance Program, and the Incident Data System of the Office of Pesticide Programs (OPP).

American Association of Poison Control Center Database

Most of the Nation's Poison Control Centers (PCCs) participate in the Toxic Exposure Surveillance System (TESS) which obtains data from 65-70 centers at hospitals and universities. PCCs provide telephone consultation for individuals and health care providers on suspected poisonings, involving drugs, household products, pesticides, etc. PCCs are staffed by Poison Information Specialists who are available 24 hours a day, 365 days a year to provide poison information, telephone management and consultation, and collect pertinent data on each exposure. Certified centers require their specialists to be trained and certified and account for 83% of the cases submitted to TESS. Until the training is completed, some calls at certified centers may be answered by individuals who have not yet completed their training and passed their certification examination. The majority of centers have a board certified physician on-call at all times with expertise in medical toxicology. The PCCs participating in TESS complete a form or computer record describing each case with standard data elements (e.g., age, route of

exposure, symptoms, medical care received, and medical outcome). For a more detailed discussion of the methodology see Blondell (1999B).

Poison Control Center Data is subject to both under- and over-reporting. Many cases seen by health care providers are not reported to PCCs, especially if the clinician is comfortable with their management. Health care providers account for about 13% of all calls to PCCs. The majority of calls come from the lay public some of whom may call when exposure is assumed but not confirmed (e.g., infant next to an open container). Lay persons may report symptoms less accurately which must be translated into specific medical terminology by Poison Information Specialists. In the discussion provided below, exposures include cases where exposure was suspected but not confirmed. Cases classified as symptomatic are those cases followed up to determine outcome with a symptom or clinical effect deemed to be related to the exposure based on the information collected by the Poison Information Specialist. For a more detailed discussion of the strengths and limitations of Poison Control Center data see Blondell (1999B) and Kingston et al. (1999).

Of the 116,225 unintentional pesticide exposures to single products in 1996, 19,033 or 16% were due to organophosphate pesticides and 5,188 or 4.5% were due to chlorpyrifos (AAPCC 1998). Given that 30% of organophosphates were not specifically identified by active ingredient, the actual number of chlorpyrifos cases reported to AAPCC is probably close to 7,000 or 6% of all the pesticide-related exposures. Many of these exposures involve small children who are exposed but never develop symptoms. Increased use of child-resistant packaging could markedly reduce these exposures. Of the cases receiving follow-up, a minority experienced moderate effects (7.7%), major or life-threatening effects (0.4%), and there was one fatality. The other 92% either developed no symptoms or minor symptoms as a result of their exposure. In 1996 there were 1,109 symptomatic cases reported to Poison Control Centers judged to have effects related to the exposure. From 1993 through 1996, there were an average of 116 unintentional chlorpyrifos cases per year with moderate to severe outcome (including one fatality) reported in residential settings.

Kingston et al. (1999) reviewed Poison Control Center data for chlorpyrifos for the ten year period 1985 through 1994. This study found that only 2.9% of the accidental/unintentional exposures reported significant outcomes, defined as a medical outcome of moderate, major, or fatal. A comparison was made based on data from 1990-1991 between unintentional exposures to chlorpyrifos (8,835 exposures), all insecticides (95,398 exposures), and all non-pharmaceutical exposures (2,082,751 exposures). Chlorpyrifos was responsible for 21% more cases with significant medical outcome than insecticides as a group and 18% more cases with significant medical outcome when compared to all non-pharmaceuticals. Based on these comparisons and the finding that fewer than 6 serious cases were reported per million pounds of sold, the authors concluded that chlorpyrifos "appears to have a comparable and acceptable safety profile." A more detailed review of recent data, presented below, agrees with this conclusion in part. However, there was some evidence of increased risk associated with certain factors including environmental residues, duration of effects, and application by a Pest Control Operator.

Poison Control Center data combined for the years 1993-1996 was examined to determine hazards from organophosphate pesticides used in residential settings (Blondell 1999). Thirteen organophosphate insecticides were analyzed with at least 100 exposures reported over the four year period. Five measures were selected by HED to assess the amount of hazard associated with chlorpyrifos relative to other insecticides, restricting the analysis to unintentional exposures in residential settings, involving a single product. These were: percent of all cases that were seen in a health care facility; percent of cases seen in health care facility admitted to a hospital; percent of cases seen in a health care facility admitted to critical care; and of those case receiving follow-up to determine outcome, percent with symptoms and percent with life-threatening symptoms.

The risk from chlorpyrifos exposures, as determined by the five measures described above, was very similar to that for other organophosphates insecticides used in residential settings for both children and adults. The one exception to this was the percent of cases with outcome determined in adults and older children that resulted in a fatal or major (life-threatening) outcome. Chlorpyrifos had the highest percentage (0.456%) of any of the 13 organophosphates for life-threatening or fatal effects which was 50% higher than the percentage reported for non-organophosphate pesticides. From 1993 through 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. Of the 34 life-threatening cases, 16 involved ingestion and the rest involved either inhalation (10 cases), ocular and/or dermal routes of exposure (5 cases), or a combination (3 cases).

The ability of chlorpyrifos to cause major effects by inhalation, dermal, or ocular routes of exposure has been in question. Specific information on symptoms was examined to see what, if any, life-threatening symptoms had been reported to confirm the classification as a major medical outcome. Among the 10 cases involving only the inhalation route, there were 2 cases that reported respiratory arrest and 1 case with paralysis. Among the 5 cases with dermal or ocular exposure, there was one case with respiratory depression and multiple seizures. And among the 3 cases with combined routes of exposure other than ingestion, there was one case with coma and multiple seizures. Thus only 5 of the 18 cases had specific symptoms reported that were consistent with a life-threatening effect, calling into question the classification of the remaining 13 cases. None of the cases had effects classified as "anticipated permanent" which is the other justification for assigning "major" to the medical outcome. Further confirmation of Poison Center records would be desirable to assure that these cases have not been miscoded. Nevertheless, these data do suggest that inhalation or dermal exposure can lead to life-threatening effects.

Other measures of chlorpyrifos risk did not differ much from the other organophosphates used in residential settings. However, organophosphates as a group pose a greater hazard, especially to young children under six years of age, than other pesticides (Blondell 1999). Children under six were three times more likely to be hospitalized, five times more likely to be admitted for critical care in an intensive care unit (ICU), and three times more likely to have

experienced a life-threatening outcome or death when exposed to an organophosphate than when exposed to non-organophosphate pesticides. Adults and older children were 50% more likely to be hospitalized and 72% more likely to be admitted to an ICU if exposed to an organophosphate. The likelihood of adults and older children getting symptoms including life-threatening effects was about the same for organophosphates as for non-organophosphate pesticides.

One measure of a pesticide's potential hazard is the frequency of cases due to exposure to residues left after application or use. The category environmental exposure is used by Poison Control Centers to capture this kind of hazard. Chlorpyrifos ranked third for serious outcomes from environmental residues among 13 organophosphates used in a residential setting (Blondell 1999). Environmental residues accounted for 15% of the chlorpyrifos exposures and 30% of the chlorpyrifos cases with serious outcome (moderate or life-threatening) which was twice as much as reported for non-organophosphates.

Another measure of potential hazard is the reported duration of effects once an individual develops symptoms. Note that most cases do not receive sufficient follow-up to determine whether effects persist or new, latent effects develop. Three percent of symptomatic chlorpyrifos cases report effects lasting longer than a week and one percent report effects lasting longer than a month, substantially more than reported for most other pesticides (Blondell 1999). Chlorpyrifos ranked first for effects persisting longer than a week (more than twice as likely as non-organophosphates) and second for effects lasting longer than a month (nearly three times as likely as non-organophosphates). This finding is consistent with an earlier review that suggested that chlorpyrifos may be a cause of chronic neurobehavioral effects in some subset of sensitive people who have been poisoned by this compound (Blondell and Dobozy 1997). However, prospective follow-up of these cases is needed to confirm what type of effects are occurring and what proportion of them are due to irritative effect of a persistent solvent odor.

For both adults and children, the number of symptomatic chlorpyrifos cases per million containers estimated in U.S. homes was about the same as for all organophosphates (Blondell 1999, Whitmore et al. 1992). For children under six years of age, there were 12.9 symptomatic cases (1993-96) in residential settings per million containers estimated in U.S. homes (1990) compared to 11.2 for all 13 organophosphates. For adults and children six years old or more, there were 44.2 symptomatic cases per million containers, compared to 43.7 for all organophosphates. Ratios calculated for all insecticides combined were 13.4 for children under age six and 41.4 for adults and children over age six. Thus, the ratio of symptomatic chlorpyrifos cases among children and adults to number of containers is similar to other organophosphates and other insecticides. Note that the number of containers is based on data from 1990 because data from later years is not available. It is assumed that the relative level of chlorpyrifos use reported in 1990 is representative of what would be found during the 1993-1996 time period.

Chlorpyrifos products use by Pest Control Operators (PCOs)

EPA surveyed certified and commercial pesticide applicators in five non-agricultural categories (structural, turf and ornamental, public health, right-of-way, and aquatic) in 1993 (Lucas et al. 1994). A total of 69 million pounds of active ingredient for all pesticides were estimated in use, including 14.4 million pounds of organophosphates (OP) or 20.8% of the total. Over 90% of the OP insecticide use is accounted for by just three active ingredients in that year: chlorpyrifos (54%), malathion (30%), and diazinon (7%).

For the purposes of estimating hazard of PCO use or consumer use, products in the AAPCC database were divided into whether they were likely to be used by PCOs or homeowners (AAPCC 1998). Undoubtedly some misclassification occurred with products in both lists. Homeowners rarely use pesticides intended solely for use by PCOs, and PCOs often use products that are primarily used by homeowners. However, the misclassification that resulted would likely dilute the comparison between the two groups rather than making it stronger. Table 1 reports the number of incidents on which calculations are based for chlorpyrifos. Tables 2 and 3 report the five measures of risk for children under six years of age and adults and older children. The bottom line in Tables 2 and 3 give the ratio of the percent for PCOs compared to the percent for non-PCO products.

Table 1. Number of exposures, symptomatic cases (life-threatening/fatal cases listed in parentheses), seen in a health care facility (HCF), or hospitalized (ICU cases in parentheses) for chlorpyrifos products used by Pest Control Operators and homeowners, Poison Control Centers 1993-1996.

Product type/ Age Group	Exposures	Symptomatic (Life-thr.)	HCF	Hospital. (ICU)
PCO/Child	273	53 (2)	56	16 (8)
Non-PCO/Child	7172	604 (4)	622	60 (26)
PCO/Adult	821	272 (2)	185	19 (8)
Non-PCO/Adult	4517	1598 (11)	817	66 (25)

Table 2. PCO compared with non-PCO use of chlorpyrifos by percent residential cases seen in a HCF, hospitalized, ICU, with related symptoms, and with major or fatal medical outcome for **children under age six**, PCCs 1993-1996.

Pesticide Type	% seen in a HCF	% Hospit-alized/ICU	% with symptoms	% major or fatal
PCO Use	20.5	28.6/14.3	38.1	1.44
Non PCO Use	8.7	11.8/9.6	18.2	.12
Ratio PCO/Non-PCO	2.4	2.4/1.5	2.1	12.0

Table 3. PCO compared with non-PCO use of chlorpyrifos by percent residential cases seen in a HCF, hospitalized, ICU, with related symptoms, and with major or fatal outcome for **adults and children six years and older**, PCCs 1993-1996.

Pesticide Type	% seen in a HCF	% Hospit-alized/ICU	% with symptoms	% major or fatal
PCO Use	22.5	10.3/4.3	76.2	.56
Non PCO Use	18.1	8.7/3.1	72.8	.50
Ratio PCO/Non-PCO	1.2	1.2/1.4	1.0	1.1

Table 1 shows that 9 percent of chlorpyrifos exposures were due to PCO products, but 21-24% of the life-threatening/fatal cases, hospitalized cases and cases seen in an ICU were due to PCO products. Tables 2 shows a much greater risk for children under six years of age exposed to products used by PCOs and containing chlorpyrifos. Adults, on the other hand, had only a slightly greater risk from PCO products than from products likely to be used by consumers. Note that the number of cases involving these PCO products is relatively small compared to consumer products. Of the total 7,445 exposures involving children under age six, just 4% were due to products known to be used primarily by PCOs. For adults and children over six, 15% of the 5,338 exposures examined involve PCO products.

Duration of effects was considered for PCO products for chlorpyrifos. There were 26 cases that had symptoms reported lasting longer than one week, which amounts to 7.9% of the 329 cases that were symptomatic, a percentage that was six times higher than for non-organophosphates (AAPCC 1998). Of these 26 cases, 9 had symptoms longer than one month, which amounts to 2.7% of the symptomatic cases, a percentage that was 8 times higher than non-

organophosphates. In some cases persistent symptoms may have been the result of a persistent odor resulting from the application by the PCO. Symptoms such as fatigue, eye irritation, throat irritation, difficulty breathing, and nausea have been reported from agricultural applications of the organophosphate DEF, which are believed to be largely due to odor rather than systemic inhibition of cholinesterase (Scarborough et al. 1989). This is likely a factor in many of the PCO-related cases, however, most of the symptoms reported appear to have been neurological, which is consistent with neurobehavioral deficits reported in studies of chronic effects of organophosphate poisoning (see below). Prospective follow-up of the cases reporting symptoms to Poison Control Centers is needed to determine their persistence, incidence, and severity of chronic complaints. Such a prospective study should try to assess what mechanism is responsible for the development of chronic problems including whether these effects are related to cholinergic effects on the brain, some type of hypersensitivity, or psychosomatic reactions perhaps related to a conditioned response to the odor.

There was an average of 274 exposures per year reported for adults and children involving PCO products containing chlorpyrifos. Though the number of exposures is relatively small, the increased risk of serious effects requiring hospitalization and admission for critical care is significant.

California Pesticide Illness Surveillance System

Cases of health effects attributable to exposure to chlorpyrifos used agriculturally, alone or in combination, reported to California Pesticide Illness Surveillance Program from 1982-1992 were reviewed. Activity (type of work being performed during exposure), for purposes of this review, was categorized as applicator, residual, mixer/loader, coincident and other (combined categories).

During the years 1982 through 1992, there were 100 cases in which chlorpyrifos was used alone or in combination, but was judged to be responsible for the illness (Blondell and Dobozy 1997). The following conclusions were drawn from the analysis of these 100 cases:

1) The applicator activity category was most frequently associated with adverse health effects, accounting for 38% of the cases where chlorpyrifos was considered the primary pesticide associated with the illness. Drift was the second largest category with 35% of the incidents. However, half of the drift cases were due to a single incident in an orange grove in 1989. Note that many cases of drift or exposure to residue in field workers may go unreported because of disincentives associated with seeking medical care and lack of physician reporting.

2) Over one-half of all incidents were systemic poisoning involving applicators and those directly exposed to spray drift. This indicates that when formulated for application, chlorpyrifos exposure can lead to poisoning.

3) The data (number of cases, categories most frequently reported) are fairly consistent from year to year, with the exception of the 18 cases due to one drift incident in an orange grove in 1989.

4) Of the 35 cases involving skin, eye, or respiratory effects, 71% were pesticide handlers, either applicators or mixer/loaders.

5) The number of systemic poisoning cases per 1000 applications ranges from 0 to 0.55 from 1982 through 1988. This is fairly consistent with the median (0.41) reported for 28 insecticides analyzed as part of the acute worker risk analysis for the years 1982-1989. Data on usage suggest that only about one-half of the applications were reported prior to 1989, when only commercial and restricted applications had to be reported. The ratio of chlorpyrifos poisoning to number of applications was similar to that of most of the other 28 insecticide alternatives. HED concludes that limited available data on chlorpyrifos do not demonstrate an excess risk for agricultural handlers or workers relative to other insecticides, but HED does recommend that its risks be mitigated where practical as part of the overall approach of the Acute Worker Risk Strategy.

<u>California Chlorpyrifos Illnesses Involving Structural PCOs</u>

A total of 304 incidents received by the California Pesticide Illness Surveillance Program involving exposure to chlorpyrifos applied by Structural Pest Control Operators (SPCO) from 1982 to 1993, inclusively, were reviewed and analyzed (Blondell and Dobozy 1997). Note that one additional year of data (1993) is provided that was not available for the agriculturally-related cases reported in California. Excluding 1993, there were a total of 273 SPCO-related cases, almost three times as many as reported for agricultural use of chlorpyrifos. This is partly because more people are present during an application by an SPCO than during agricultural use. Note that SPCO cases involving exposure to non-occupational persons (residential rather than business applications) are much less likely to be reported under the California mandatory reporting requirement. Such cases would not be covered by worker's compensation and, the payment incentive for physician reporting does not apply. Therefore, these types of cases are likely greatly under-reported. On the other hand, many of the cases (exact number not known) were due to broadcast carpet or fogger uses which have since been canceled.

The 304 cases were also analyzed by activity category. In 46 of the 304 incidents (15%), there was an indication that an accident occurred which resulted in the exposure, most commonly a hose breaking. Failure to wear safety protection (mostly goggles) or lack of safety training was reported in 21 cases (7%). The comments sections also contain several incidents where pesticide application was made while people were in the premises.

Upgrading requirements for certification and application should be considered for pesticides like chlorpyrifos that can result in damage to property and significant adverse health

effects that may cost thousands of dollars per case. Removing bystanders from the immediate site of application and thorough ventilation would prevent a large number of these cases.

Washington State Health Department

Washington State has had an ongoing pesticide poisoning surveillance program in place which has consistently captured information on pesticide exposures since 1995. From 1995 through 1998 there were 880 incidents of human exposures with health effects possibly, probably or definitely related to pesticide exposures. Of these 880, 95 or 11% are reported as involving chlorpyrifos. Excluding cases involving tank mixes or two or more products, there were 40 cases (7 agricultural and 33 non-agricultural) involving chlorpyrifos products alone. Of the 40 human incidents involving chlorpyrifos alone, half resulted from exposures to residues from a residential application. Note, however, that only 1 of these cases had sufficient documentation to be classified as a probable case. The rest were classified as possible. Eleven cases involved handlers who applied or mixed the product (1 definite, 2 probable, and 8 possible) and four were due to drift from a nearby application (1 probable and 3 possible).

Incident Data System Reports

Since June 1992 the U.S. Environmental Protection Agency has maintained a computerized file of all incident reports submitted to the Agency. Most reports come from the pesticide registrants which are required to report suspected incidents under section 6(a)(2) of FIFRA. Since June of 1992, there have been over 3,000 new reports alleging adverse health effects in humans. Just over a third of these reports involve products used primarily by PCOs. There was insufficient documentation confirming exposure or health effects to warrant a detailed analysis of most of these reports.

More comprehensive information has been required under the revised guidelines for reporting of incidents issued by EPA in 1998. These requirements only apply to the manufacturer of the pesticide and not to reports submitted by the public or other non-registrants. From 1998 through 1999 Dow AgroSciences submitted 147 new reports of human incidents involving single products containing chlorpyrifos. There were 11 deaths reported, five of which occurred during the two year period 1998-1999. The other six occurred from 1994 to 1996. Two of the deaths, one suicide and one unintentional (the 22 month old boy described elsewhere in this report) appeared to be related to chlorpyrifos ingestion. One additional suicide could not be confirmed as involving chlorpyrifos. There were a number of cases involving legal suits related to cancer, heart attack, kidney failure, and premature death of an infant that had no significant supporting data to indicate that chlorpyrifos was responsible for the deaths. Most of the other reports also lacked evidence that would lead one to believe that chlorpyrifos was a likely cause of the alleged effects. Fifteen of the 147 reports included reports of chronic symptoms which are discussed elsewhere in this report.

National Pesticide Telecommunications Network

Chlorpyrifos was the highest ranked active ingredient each operational year from 1995 through 1998 with 897 human incidents reported to the National Pesticide Telecommunications Network (NPTN). Chlorpyrifos alone accounted for over a quarter of the total of 3,284 human incidents reported for the top 25 active ingredients during those four years. A relatively small number of these case had sufficient documentation of exposure or effects to be classified by a certainty index of probable or definite. NPTN defines "definite" as measured concentrations with observed effects that are consistent with the known toxicology of the pesticide. NPTN defines "probable" as no measured residues, probable exposure, and consistent effects. Of the 897 chlorpyrifos cases, 158 were considered to be probable or definite, accounting for 31% of the 505 incidents reported for the top 25 pesticide active ingredients during those four years.

Literature Reports on Acute Effects

Hodgson et al. (1986) reported on five office workers poisoned primarily by inhalation exposure to chlorpyrifos. Exposure occurred through an air intake vent on a Friday, and 2 of the workers were also present for 8 hours on Saturday and Sunday. All five workers reported symptoms the following Monday. Symptoms and number of individuals reporting them were: chest tightness (3), cough (2), visual symptoms (2), drooling (3), sweating (3), nausea (4), diarrhea (4), abdominal pain (3), weakness (4), fatigue (5), restless (2), anxiety (4), confusion (2), and disturbed speech (1). Measurements of red blood cell cholinesterase levels found that recovery to normal took up to 80 days. Three weeks later one person reported numbness and tingling in the fingertips of both hands which lasted one week. According to Berger and Schaumberg (1994), a case of paresthesia involving only the upper extremities should not be regarded as evidence of toxic neuropathy. Hodgson states that this application was in conformance with label directions and recommends that people stay outside of structures when they are being treated with chlorpyrifos and that a reentry interval be established before workers are allowed back inside. No residues were found on surfaces at this site 2 weeks after the application.

Dunphy et al. (1980) reported a case of an 11 day old boy who was exposed to food and clothing in his home that had been contaminated with measurable levels of chlorpyrifos. His symptoms included cyanosis, miosis, excess salivation, vomiting, lethargy, and respiratory arrest. Red blood cell cholinesterase levels were reported to be 50% below normal in this life-threatening poisoning. This unusually severe case in such a young child suggests that children and infants may be far more susceptible to chlorpyrifos poisoning than adults.

Zweiner and Ginsburg (1988) reported on 37 children seen in one hospital in Texas, ranging in age from 1 month to 11 years, with moderate or severe organophosphate poisoning. Ingestion of stored liquid was involved in 76% of cases and playing on carpet or floor after application was involved in 14% of cases. The initial diagnosis was not recognized as OP poisoning in 16 of the 20 children transferred for care. The most commonly reported symptoms

included miosis (73%), excessive salivation (70%), muscle weakness (68%), respiratory distress (59%), lethargy (54%), nausea/vomiting (32%), seizures (22%) and coma (22%). Twelve (38%) of the children required mechanical ventilation to maintain respiration. Six of the total 37 cases were reportedly due to chlorpyrifos, more than any other organophosphate. Three of six chlorpyrifos cases were life threatening due to coma or respiratory arrest (Ginsburg, personal communication). The authors concluded that bradycardia and muscle twitching were less likely in childhood poisonings than in adults, but that seizures were more common in children. They noted that all children who had seizures also had respiratory insufficiency and that, therefore, hypoxia might be the underlying cause of the seizures.

Chronic Effects

Summary

HED concludes that chlorpyrifos may be a significant cause of chronic neurobehavioral effects among people who were poisoned. Further study is needed to determine the prevalence, severity, and persistence of these effects, as well as the occurrence of self-reported multiple chemical sensitivity. The possibility that chlorpyrifos may also be a cause of peripheral neuropathy at sub-lethal doses has been suggested by a number of anecdotal and published reports but not well-substantiated by controlled studies.

Case reports

Dr. Sheldon Wagner has served as a medical consultant for cases of illness potentially related to pesticides since the late 1980s. The Office of Pesticide Programs at EPA has provided funding for this consultation. In the first 20 months, Dr. Wagner consulted on over 300 referrals. The second most frequently raised concern, after chlordane, was chlorpyrifos which was responsible for 34 inquiries. Dr. Wagner noted, "The most difficult problem has been encountered with chlorpyrifos. There have been 34 inquiries about this insecticide. The clinical problems most commonly raised have been complaints of long-term illness following acute exposure and/or intoxication" (Wagner 1990).

With the ban on chlordane in 1988, chlorpyrifos has become the number one source of referrals to Dr. Wagner. More recent reports specify the types of problems that are most common: An individual whose home was treated developed symptoms consistent with organophosphate poisoning. Dr. Wagner noted that the manner in which the PCO applied the product may have contributed to the problem: "It is my judgment that the label for Empire-20 is not clear as to whether this compound can be used in food dispensing areas such as the kitchen - as it was in this particular case. Furthermore, the label is also incorrect stating that any area in which the product has been applied may be treated simply by water" (EPA Case 93-183, Wagner 1993).

Another case reported in a school illustrates the potential for major costs associated with misapplication of Dursban: "This is another episode of acute illness developing in children as the result of pesticide treatment to a school in which the formulation was applied while children and teachers were in the building. Additionally, as is not unusual, the heat duct system became contaminated and illness became more severe when the heating system was turned on. This problem is similar to many other cases . . . many times the recommendation must simply be to put in an entirely new heat duct system" (EPA Case 93-211, Wagner 1993).

The following typical case of misuse was reported in 1994:
"Her home was treated by 'crack and crevice' in an excessive manner whereby Dursban (chlorpyrifos) was applied and freely flowed down the walls and also got onto furniture. It also was applied in an eating area. She developed complaints of dyspnea and diarrhea. She eventually was hospitalized with a diagnosis of organophosphate intoxication (EPA Case 94-091, Wagner 1994a)". Summarizing the chlorpyrifos problem in 1994, Dr. Wagner concluded: "The most frequent organophosphate concern continues to be from chlorpyrifos use within homes, not from agricultural practices" (Wagner 1994b).

Though rarely reported, the following case suggests chlorpyrifos potential to bring on asthma:

> This was a child with no history of allergic or atopic problems. His room was treated with Dursban and he immediately developed an asthmatic syndrome which has been persistent. Documentation of an acute Reactive Airway Dysfunction Syndrome is excellent and correlates extremely well with the temporal relationship to the Dursban formulation (Wagner 1995).

In a case reported directly to EPA by a physician, a worker was exposed to Dursban granules while mowing the lawn all day long without wearing a shirt. The high humidity combined with perspiration led to significant dermal exposure and symptoms consistent with organophosphate intoxication. One year later the worker still complained of persistent headaches, extreme muscle weakness, and problems with memory, concentration, confusion, irritability, and depression. Labels for chlorpyrifos products applied to lawns need to be modified so that people who may come into substantial contact with chlorpyrifos are properly warned. This may be done by posting a restricted entry interval or assuring that the application is sufficiently diluted by rain or watering. In circumstances where it is not possible to prevent reasonably foreseeable 'substantial contact', chlorpyrifos application should be prohibited.

Dow AgroSciences reported 147 new cases involving chlorpyrifos products alone to EPA in 1998 and 1999. Of these, 15 reported two or more persistent symptoms consistent with chronic neurobehavioral effects. Note that some of these reports overlap those reported elsewhere in this summary, including reports from Dr. Wagner and Dr. Kilburn (1999). Two of the reports came from individuals who reported an occupation of Pest Control Operator. Note that the cases reported by Dow AgroSciences did not have documentation of the exposure or the effects sufficient for confirmation.

As a result of public comment on the preliminary risk assessment on chlorpyrifos, EPA received a number of reports from individuals alleging chronic effects from exposure. There were 61 people with symptoms consistent with chronic effects of organophosphate poisoning. None of these reports noted or supplied medical documentation to substantiate the reported complaints. A total of 45 people or 74% had symptoms of chronic neurobehavioral effects, in that they reported at least one of the following 10 persistent symptoms: headaches, muscle weakness, muscle aches/pains, fatigue, visual difficulties, memory problems, inability to concentrate, confusion, irritable, or depression. These 10 symptoms are the most common reported chronic neurobehavioral effects reported in the scientific literature in case-control, cross-sectional, and case series reports. Overlapping this group was another group of 24 people (39% of the total) who complained of unusual chemical sensitivities or multiple chemical sensitivity (MCS). Another 16 people (26% of the total), also overlapping those with chronic neurobehavioral effects or MCS, reported at least one symptom (e.g., paresthesia in extremities, difficulty walking) consistent with peripheral neuropathy. Note that all of these reports except three are new to the Agency since the January 14, 1997 "Review of Chlorpyrifos Poisoning Data" (Blondell and Dobozy 1997) and supply additional anecdotal evidence that chlorpyrifos poisoning can lead to chronic effects in susceptible individuals.

Another 12 people supplied medical documentation to substantiate the reported complaints. A total of 11 people or 92% had symptoms of chronic neurobehavioral effects. Overlapping this group was another group of 8 people (67% of the total) who complained of unusual chemical sensitivities or MCS. Another 3 people (25% of the total), also overlapping those with chronic neurobehavioral effects or MCS, reported symptoms consistent with peripheral neuropathy. Note that all but one of these reports are new to the Agency since the January 14, 1997 "Review of Chlorpyrifos Poisoning Data" and these reports also supply additional anecdotal evidence that chlorpyrifos poisoning can lead to chronic effects in susceptible individuals.

The duplicate case includes additional medical documentation not available for the 1997 review. This well documented case includes a diagnosis of pesticide poisoning when initially exposed and medical diagnoses of chronic effects from four physicians including:
1. Polysensory neuropathy, myelopathy, and encephalopathy all probably secondary to toxic exposure.
2. Progressive neuropathy which is primarily of the sensory type.
3. Chemical encephalopathy and delayed neuromyopathic syndrome due to Dursban.
4. Polyneuropathy and encephalopathy and peripheral neuropathy confirmed by testing felt to be secondary to organophosphate exposure.
These physicians suggest that chlorpyrifos may have been a cause of either a peripheral neuropathy or polysensory neuropathy which was not supported by the evidence available for the "Review of Chlorpyrifos Poisoning Data" completed on January 14, 1997. This one well documented case plus the additional anecdotal reports above and the report by Kilburn cited below suggest that chlorpyrifos may be a cause of peripheral neuropathy predominantly of the polysensory type.

Multiple chemical sensitivity cases reported to EPA and NPTN

Partly as a result of media coverage, a number of individuals have contacted the EPA or the NPTN to report that they have developed an intolerance to chemical exposures (commonly, pesticides, perfume, petroleum by-products, paint, solvents, and cleaning substances) after an over-exposure to chlorpyrifos (Blondell and Dobozy 1997). These individuals report developing symptoms after exposure to previously tolerated odors and chemicals. Symptoms may include fatigue, headache, shortness of breath, muscle aches and pains, nausea, gastrointestinal distress, and mental problems including memory loss, confusion, and depression. Of the 59 cases that were interviewed, 85% reported that the chlorpyrifos application was by a Pest Control Operator and 76% of the cases were female. The median age of was 40. Miller and Metzel (1994) reported on 37 cases of chemical sensitivity that developed after over-exposure to organophosphates, half of which were reportedly due to chlorpyrifos. Various hypotheses have been advanced to explain multiple chemical sensitivity ranging from a psychosomatic response brought on by a fear of chemicals to a physiological changes in the brain. One recent review suggests that a physiological basis for MCS is more likely (Graveling et al. 1999). More research is needed to resolve the controversy about causal mechanisms.

From 1984 through 1990 the National Pesticide Telecommunications Network (NPTN) received 1,022 calls complaining of unusual chemical sensitivity to pesticides (Blondell and Dobozy 1997). Many, perhaps the overwhelming majority of these calls, involved multiple chemical sensitivity type problems. Chlorpyrifos was the leading pesticide listed for chemical sensitivity, accounting for 158 calls during the 7 year period, or 15% of the total. Data from the 1990 survey of home and garden pesticide use permits a comparison based on the number of containers in U.S. homes (Whitmore et al. 1992) . The total number of pesticide containers was 247,650,000 and the total for chlorpyrifos was 16,652,000. The ratio of calls per million containers in U.S. homes was 9.5 for chlorpyrifos (158/16,652,000) and 4.1 for all pesticides (1,022/247,650,000). Although these ratios do not take into account the number of PCO applications in the home, it does appear that the chemical sensitivity problem associated with chlorpyrifos is not due to its widespread use.

Literature on chronic effects

Kilburn (1999) reported on 22 patients seen from 1991 to 1997 who were either referred by attorneys (12 cases) or self-referred (10 cases). Patients received a variety of neurological and neurobehavioral tests including tests of balance, reaction time, vision, grip strength, memory, cognition and mood. Three staff performed the testing on the 22 subjects and 264 non-exposed subjects (referents) recruited at random from voter registration roles in Arizona and Louisiana. Mean scores and distributions were calculated for the two groups (exposed and referents) and stepwise regression in the non-exposed group was used to estimate the predicted test result taking into account factors such as sex, age, and education level which are known to effect test results. Subjects also completed a questionnaire concerning 35 common health complaints rated on a scale of 1 (rare) to frequent or daily (11).

Nineteen of the 22 patients were exposed indoors in offices or homes where pesticides containing chlorpyrifos were applied (Kilburn 1999). Two other patients were pesticide applicators with 5-6 years of experience and one was an agricultural worker exposed during aerial spraying. Eight patients reported single exposures lasting no more than a few days and the rest had exposures that lasted or repeated over a period of weeks, months, or years.

There were no measurements taken that confirmed the presence of chlorpyrifos in the air of the 19 premises where exposure occurred (Kilburn 1999). However, six patients had detailed schedules of pesticide applications and an additional four patients had measurable levels of chlorpyrifos in clothing or on their carpet. Another seven patients reported reentering the treated structure after application had taken place and one patient was present during and for three days following an application to her motel room.

Half of the patients had evidence of peripheral neuropathy manifested by weakness and sensory changes (Kilburn 1999). Significant differences were noted between exposed and referents on tests of balance, reaction time, vision, grip strength, memory, cognition, and mood. Among the 35 common health complaints, the top four complaints among the exposed were recent memory loss (mean score 8.4), loss of concentration (mean score 8.2), headache (mean score 7.7), and extreme fatigue (mean score 7.5). Each of these symptoms was statistically higher (probability < 0.0001) than the referents who had mean scores ranging from 3.6 to 4.9 less than the means for the exposed.

Other explanations for the significant differences were ruled out such as pre-existing nervous system disease, head trauma, or prolonged anesthesia (Kilburn 1999). Two patients, an applicator and an agricultural field worker, reported exposure to other pesticides and chemicals suspected to cause neurological or neurobehavioral effects. The total number of abnormalities found in self-referred cases was not significantly different from the number found in lawyer-sponsored cases. This plus the use of the best or the most representative result from multiple trials diminish the likelihood that results were due to intentional falsification or malingering. Nevertheless, it must be acknowledged that exposed subjects were self-selected or attorney-selected and therefore cannot be regarded as representative of all patients experiencing chronic effects from chlorpyrifos. Caution must be used before generalizing the results from this study to other populations of exposed subjects.

Kaplan et al. (1993) reported that 5 of their 8 subjects with peripheral neuropathy experienced problems with memory and confusion suggesting central nervous system dysfunction. Other reviewers have questioned the diagnosis of peripheral neuropathy in these cases. Of the five cases with chronic neurobehavioral effects, four reported that they recovered after a period of months or years.

Rosenthal and Cameron (1991) reported that a 64 year old male had a termite application with chlorpyrifos and experienced severe abdominal pain, nausea, headache, difficulty breathing, fatigue, irritation of the eyes, nose and throat, anxiety, and irritability. Many of these symptoms

reportedly continued for 2 years whenever he was present in the home. He also reported developing a sensitivity to new furniture and carpet odors.

Rouche (1988) reported on a 57 year old physician who was exposed to Dursban and Ficam (bendiocarb) when airing out a cabin that was treated monthly with these pesticides. Her initial symptoms included nausea, abdominal cramps, diarrhea, salivating, sweating, metallic taste in the mouth, tightness in chest, palpitations blurred vision, muscle weakness, twitching in legs, and tingling on bottom of feet. Persistent symptoms included leg weakness, decreased strength, muscle twitching, and reduced sensory response in the legs. She was diagnosed with peripheral neuropathy. This case was reported in the popular media, but discussions with one of her treating physicians have confirmed the information.

Steenland et al. (1994) performed a case-control study on 128 workers poisoned by organophosphates. Ten of these subjects had primary exposure to chlorpyrifos at the time of poisoning and an additional seven cases had poisoning from chlorpyrifos and some other organophosphate insecticide. Among those with primary poisoning from chlorpyrifos, they had significantly worse peroneal nerve conduction velocity and ulnar sensory amplitude. Those with any exposure involving chlorpyrifos reported more tension on mood scales and performed worse on tests of finger vibrotactile sensitivity.

Steenland et al. (2000) performed another case-control (cross sectional) study of neurologic function in 191 current and former termiticide applicators in North Carolina with an average of 2.4 years applying chlorpyrifos. Exposed cases were compared to 106 friends and 83 blue-collar workers employed by the State government. About half of the exposed were asked to bring a friend of the same gender and same age (within 5 years). Among applicators reporting current exposure to chlorpyrifos, within the past week, urinary levels of TCP (a metabolite largely specific to chlorpyrifos) averaged 630 ug/l, which confirms relatively high exposure for this kind of work.

The authors (Steenland et al. 2000) concluded "this cross-sectional study of workers exposed to chlorpyrifos . . . found few exposure related effects for most tests, including a clinical exam. However, the exposed did not perform as well as the non-exposed on pegboard turning tests and some postural sway tests. Furthermore, exposed subjects reported more symptoms than non-exposed subjects; this is a cause for concern because previous studies lend some support to this finding." Study subjects were asked about 24 symptoms and how bothersome they were in the past month. Ten percent or more of the exposed subjects reported the following 8 symptoms, as occurring moderately, quite a bit, or extremely and at least twice as often as the controls (data provided by study authors):

1. Tired more easily than expected for the amount of work you do (exposed 26%, controls 11%).
2. Felt lightheaded or dizzy (exposed 10%, controls 5%).
3. Had difficulty concentrating (exposed 12%, controls 5%).
4. Relatives noticed that you have trouble remembering things (exposed 10%, controls 4%).
5. Had to make notes to remember things (exposed 27%, controls 12%).

6. Felt depressed (exposed 10%, controls 4%).
7. Had headaches at least once a week (exposed 18%, controls 5%).
8. Had a lower tolerance for alcohol (exposed 10%, controls 4%).
This pattern of increased problems with fatigue, concentrating, memory, depression, and headaches are consistent with the symptoms most often reported by Kilburn (1999) in his case series. The replication of reported symptoms in these two different studies as well as their prevalence in the anecdotal reports received by EPA supports the finding that chlorpyrifos is probably a cause of these chronic effects.

The absence of objective measures of these defects in Steenland et al. (2000) may be related to the lack of appropriate tests. In a review sponsored by the National Research Council, Hanninen points out that more sensitive tests are needed to assess memory deficits, more valid and practical tests are needed to assess attention, and more comprehensive tests are needed to measure affect or mood states and personality (Hanninen 1990).

Four percent of the exposed cohort reported experiencing acute poisoning from exposure to chlorpyrifos. "Eight men who reported past chlorpyrifos poisoning had a pattern of low performance on a number of tests, which is consistent with prior reports of chronic effects of organophosphate poisoning." (Steenland et al. 2000). Finally, the study noted the following reservation, partly due to the relatively heavy exposure experienced by study participants, "Although this was a relatively large study based on a well-defined target population, the workers we studied may not be representative of all exposed workers and caution should be exercised in generalizing our results." (Steenland et al. 2000). These findings are 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).

Thrasher et al. (1993) reported on 12 chlorpyrifos victims 1-4.5 years after exposure. Their chief chronic complaints included fatigue, headaches, dizziness, loss of memory, joint and muscle pain, gastrointestinal disturbances, and respiratory symptoms. Eleven of the 12 cases involved application by a Pest Control Operator. A number of immunologic differences were reported in this population, but unfortunately these results have not been duplicated by other labs and recent literature has raised questions about the significance of the lab techniques employed.

Case follow-up studies (Holmes and Gaon 1957, Gershon and Shaw 1961, Tabershaw and Cooper 1966, Metcalf and Holmes 1969, Hirshberg and Lerman 1984) and case-control studies (Savage et al. 1988, Rosenstock et al. 1991, Steenland et al. 1994, Stephans et al. 1995) have been conducted on individuals poisoned by other organophosphate insecticides that suggest that a portion of those who are poisoned will develop chronic neurobehavioral effects. Reviews by Karalliedde and Senanayake (1989), Ecobichon (1994), the U.S. Congress Office of Technology Assessment (1990), the World Health Organization (1990), Jamal (1997) and the United Kingdom Department of Health's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (1999) support this finding.

In their review, Karalliedde and Senanayake (1989) concluded, "Behavioral changes have been documented following acute or chronic OP poisoning. These symptoms may take months to regress . . . some or all of the following observations have been made: (1) Impairment of vigilance, information processing, psychomotor speed and memory. (2) Poor performance and perception of speech. (3) Increased tendency to faster frequencies and higher voltages in EEG records". Ecobichon's 1994 review of organophosphates and neurological disease concluded "Sufficient anecdotal information can be found in the medical literature to signify that there are persistent and serious complaints lasting from 6 months to several years and, possibly, forever". The World Health Organization (1990) suggests that 5 percent of occupational poisonings due to organophosphates result in these effects. The Office of Technology Assessment of the U.S. Congress (1990) concludedn: "Case reports and studies of acute poisonings of agricultural and other workers indicate that 4 to 9 percent of the acutely poisoned individuals experienced delayed or persistent neurological and psychiatric effects." These effects include "irritability, depression, mood swings, anxiety, fatigue, lethargy, difficulty concentrating, and short-term memory loss."
In the most recent review, the United Kingdom Department of Health's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (1999) concluded, in part,

> "The balance of evidence supports the view that neuropsychological abnormalities can occur as a long-term complication of acute OP poisoning, particularly if the poisoning is severe. Such abnormalities have been most evident in neuropsychological tests involving sustained attention and speeded flexible cognitive processing ("mental agility")."

The reports cited above provide evidence of neurobehavioral damage consistent with that reported for other organophosphate insecticides. The association is fairly specific and has been observed in a variety of different populations. Such effects are biologically plausible based on animal studies showing direct effects on the brain. Taking these case reports and studies together, it is reasonable to conclude that some subset of poisoned subjects probably experience persistent neurobehavioral effects as a result of their exposure to chlorpyrifos. Research specific to chlorpyrifos with laboratory evidence to confirm the exposure is needed to confirm this finding. The possible role of the odoriferous carrier which has been hypothesized to lead to a conditioned response should also be investigated.

Reports of Birth Defects

There have been reports in the literature (and reports sent to EPA suggesting an association between chlorpyrifos exposure and birth defects (Blondell and Dobozy 1997, Jackson et al. 1999, Sherman 1996, 1997, 1999). These cases have been reviewed for EPA by the Division of Birth Defects and Developmental Disabilities at the National Center for Environmental Health, one of the Centers for Disease Control. Based on their review and other information, HED concludes the available evidence does not support a finding of teratogenicity based on human epidemiology studies and case reports.

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ATTACHMENT

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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: February 3, 1999

SUBJECT: Reviews of submittals by Dow AgroSciences on chlorpyrifos

TO: Mark Hartman, Reregistration Review Branch 2
Special Review and Reregistration Division (7508C)

FROM: Jerome Blondell, Ph.D., Health Statistician
Chemistry and Exposure Branch 2
Health Effects Division (7509C)

THRU: Ray Kent, Branch Chief
Chemistry and Exposure Branch 2
Health Effects Division (7509C)

Listed below are reviews of six submittals from Dow AgroSciences concerning human evidence of adverse health effects from exposure to chlorpyrifos. The following submittals are reviewied in this memorandum: MRID Nos, 43480001, 44039901, 44186301, 44245801, and two studies with no MRID numbers, the 1997 Epidemiology Blue Ribbon Panel Report and a 1995 submittal that critiques EPA's review of neuropathy allegations due to chlorpyrifos.

Review of "Interpretation of chlorpyrifos exposure incident data" by William L. Chen submitted by DowElanco December 9, 1994. MRID no. 43480001.

This is Dow AgroSciences' review of incident data that it submitted to EPA. The same information reviewed in this document was reviewed in greater detail by the EPA's Health Effects Division (Blondell and Dobozy 1997). Therefore, only a brief summary of a couple of the pertinent points in this document will be presented here.

This document provides a brief review of the 1985-1992 data collected by the American Association of Poison Control Centers (AAPCC) on chlorpyrifos. A total of 25,995 exposures were reported in this time period including both intentional (e.g., suicide) and unintentional exposures. In 1992 chlorpyrifos accounted for 9.5% of all insecticide cases reported to AAPCC. EPA's own survey of household pesticide use (Whitmore et al. 1992) found that chlorpyrifos accounted for 16,652,000 containers out of 176,454,000 insecticide containers or 9.4%. This supports the contention that the number of chlorpyrifos exposures occurring are not out of proportion to their use when compared to other insecticides. DowElanco estimated chlorpyrifos accounted for 25% of the market share for all residential insecticides. This estimate was not supported by any data or references but is not inconsistent with reports that include both consumer use and use by Pest Control Operators (PCO). As noted by the Health Effects Division (Blondell and Dobozy 1997), exposures related to PCO use need to be considered separately from homeowner use because of the different risk factors involved.

The apparent increase in chlorpyrifos exposures from 1985 through 1992 can be explained by the increased reporting by Poison Control Centers and the increased use of chlorpyrifos. The Health Effects Division does not have any information that would suggest that chlorpyrifos incidents have increased independent of reporting and use.

DowElanco contends that odor rather than chemical poisoning may be responsible for some of the symptoms reported to Poison Control Centers. They cite the fact that 30% of the AAPCC cases were due to inhalation as supporting evidence. The Health Effects Division agrees that some of the minor symptoms such as nausea and headache may be a response to a bad odor rather than evidence of systemic poisoning due to cholinesterase inhibition. However, both headache and nausea are early signs of cholinesterase inhibition. It is not possible to say what proportion of reported cases of nausea and headache are due to odor or due to cholinesterase inhibition. Regardless of the cause, headache and nausea are adverse effects and measures to reduce their occurrence are recommended.

Review of "Critical analysis of the allegations of neuropathy due to chlorpyrifos submitted to the United States Environmental Protection Agency on November 7, 1994." submitted by DowElanco March 22, 1995. No MRID number.

This is Dow AgroSciences' review of neuropathy evidence that it submitted to EPA. The Health Effects Division reached conclusions similar to the DowElanco review of allegations of neuropathy due to chlorpyrifos. Page 44 of the Blondell and Dobozy review (1997) found only one physician-diagnosed case of mild peripheral neuropathy with below normal cholinesterase after the initial exposure and evidence of abnormal nerve conduction. Two years later this patient reportedly recovered. None of the other cases received from DowElanco provided convincing evidence of peripheral neuropathy due to chlorpyrifos exposure. However, the Health Effects Division does not agree with DowElanco conclusion that "none of the alleged neuropathies are due to exposure to chlorpyrifos". Given the absence of information and a

number of unsubstantiated anecdotal reports, a more guarded conclusion would be appropriate. Chlorpyrifos may cause a type of peripheral neuropathy, different from the organophosphate induced delayed neuropathy (OPIDN) described in the scientific literature, that has not been investigated in population studies or in individual cases. Until such comprehensive research has been undertaken the possibility that chlorpyrifos is a cause of some type of peripheral neuropathy remains an open question. The Health Effects Division did conclude that available evidence did not support the finding that chlorpyrifos was a cause of OPIDN at sublethal levels of poisoning.

Review of "An update of the morbidity experience among employees potentially exposed to chlorpyrifos" by C.J. Burns, J.B. Cartmill, B.S. Powers, and M.K. Lee submitted by DowElanco June 20, 1996. MRID no. 44039901.

This study examined 496 potentially exposed workers (423 men and 73 women) for evidence of increased illness or symptom prevalence and specifically peripheral neuropathy. To be selected employees had to work in the manufacture of the technical, granular or liquid formulations of chlorpyrifos between 1977 and 1994, inclusive. Two unexposed workers (controls) actively employed at the same location were sought for each case matched on age, race, sex, year of hire, and salary category. Workers with potential exposures or who had received a cholinesterase test, and therefore might have been exposed, were excluded from the control group. A total of 911 controls were identified, so that for 81 cases there was only one control. Tobacco and alcohol use was similar in cases and controls though no attempt was made to match on these two factors. Exposure among cases was ranked high, moderate, low, and negligible based on potential airborne and dermal exposures categories times the number of days employed in the job assignment. The majority of cases (345) were classified as moderate exposure which meant airborne exposures were between 0.03 and 0.2 mg/m^3. There were 29 workers with negligible exposure, 121 with low exposure, and only 1 case categorized as potentially high exposure. Cholinesterase results for workers correlated well with exposure classification.

A major drawback of this type of study is that the exposures under carefully controlled conditions in a manufacturing plant are atypical of what would be experienced by an end user of the final product. Workers at the DowElanco plant with exposure to chlorpyrifos are required to undergo monthly cholinesterase testing. This leads to greater worker awareness of potential risks and safer work practices than would commonly be found among end users. Though careful and appropriate effort was made to rank employees into exposure categories, it was not possible to take into account periodic incidental exposures that may have occurred at levels above the threshold to cause health effects. This means that a worker normally working in a low or moderate exposure situation, may have unusually high exposure due to a one time spill. This is a type of exposure misclassification that is to be expected in a study of this type. Another drawback of this type of study is that the number of workers studied (496) are insufficient to identify significant difference between cases and controls for relatively rare health effects. Such a study is also unlikely to measure effects that could be limited to people who are relatively

unhealthy or are unusually sensitive, because self-selection would usually prevent such people from being employed in the first place.

Significantly elevated prevalence odds ratios (OR) were reported for five conditions including: diseases of the ear (OR = 1.81, 95% confidence interval: 1.29 - 2.54); acute respiratory infections (OR = 1.49. 95% CI: 1.08 - 2.05); other diseases of the respiratory system (OR = 2.80, CI: 1.18 - 6.65); ill-defined conditions such as dizziness, fatigue, or fever (OR = 1.64. 95% CI: 1.14 - 2.37); and ill-defined conditions of the digestive system such as nausea, heartburn, or vomiting (OR = 1.66, 95% CI:1.09 - 2.55). No evidence was found for increased risk of peripheral neuropathy or reports of tingling or numbness in the extremities among cases when compared to controls.

Note that the lower estimate of the confidence interval is close to 1.0 in all cases, suggesting that some of these significant results were likely due to chance rather than a real effect of chlorpyrifos. Further, none of these associations persisted when workers were classified by exposure level or evidence from cholinesterase testing. Workers classified as having negligible exposure had higher odds ratios for four of the five disease conditions (the fifth condition had insufficient numbers to permit odds ratios being calculated) than workers with moderate exposures. One possibility that could account for such a finding is that workers affected by chlorpyrifos request to be placed where their exposure is negligible, but their symptoms persist. It might be worthwhile, if the data are available, to go back and determine whether any of the workers with health complaints in the negligible category had an initial experience with high exposure, including one time accidents that may have led to short-term but high exposure. This would help address the concerns about misclassification expressed earlier. This is particularly true for the category "general symptoms, signs and ill-defined conditions". Workers with negligible exposure had the highest odds ratio for any disease condition calculated in this study (OR = 10.85, CI: 2.95 - 40.00). Anecdotal reports have suggested that unusual fatigue (an example of an ill-defined condition) may be a persistent health effect of chlorpyrifos exposure therefore, special attention should be given to those workers in any exposure category reporting this condition.

In conclusion, the present study does not find any evidence of dose-response health effects in manufacturing workers with exposure to chlorpyrifos. Several limitations have been pointed out above that largely restrict this conclusion to the workers in the present study. The possibility that one-time incidental exposures (e.g., one time spill) lead to health effects has not been addressed by this study.

Review of "Critical review of allegations associating Dursban with human teratogenicity" by J.E. Gibson submitted by DowElanco December 23, 1996. MRID no. 44186301.

This review examines cases that came to the attention of DowElanco due to litigation which it subsequently submitted to EPA. Page 38 concludes "No human epidemiological studies suggest

any link between Dursban and birth defects, and the only study which has been conducted suggests that Dursban is not a human teratogen." The phrase "suggest any link" implies there is no evidence whatsoever, a position that the Health Effects Division does not support. However, the more important question is the weight of evidence that chlorpyrifos exposure is a cause of birth defects. The Health Effects Division arranged for a review of the same cases by the National Center for Environmental Health. Based on their review HED concluded "the available evidence does not support a finding of teratogenicity based on human epidemiology studies and case reports."

Review of "Critical assessment of report entitled 'Review of Chlorpyrifos Poisoning Data (by J. Blondell and V. Dobozy, January 14, 1997)'" by B.A. Shurdut, W.L. Chen, C.J. Burns, R.A. McCormick, R.J. Nolan, K.D. Racke. Submitted by DowElanco, March 31, 1997. MRID no. 44245801.

This is Dow AgroSciences' critique of EPA's analysis of poisoning surveillance data. None of the authors of this report appear to have particular expertise in surveillance epidemiology, the subject of their critical assessment. They have not published in the field of epidemiology in the open literature. EPA determined that this Dow AgroSciences assessment contained no new findings that warranted significant changes in EPA's conclusions or recommendations put forth in the review by Blondell and Dobozy (1997).

Some of the statements in the DowElanco review are clearly inaccurate or misleading. For example:

1. Page 9 "chlorpyrifos products have never been shown to cause human neurological injury except at lethal doses". Poisoning is a type of injury. Victims of chlorpyrifos poisoning experience neurological effects (e.g., ataxia, excess secretions, blurred vision). In addition to these temporary or acute effects, reviews by WHO (1990), Office of Technology Assessment (1990), Karalliedde and Senanayake (1989) and Ecobichon (1994) have asserted that organophosphate insecticides can cause chronic neurobehavioral effects. The case-control study by Steenland et al. (1994) suggests these effects among those poisoned by chlorpyrifos.

2. Page 9 "residential use does not result in chronic exposures". There are numerous incidents where measurable levels of chlorpyrifos, well above ambient background, were found months after the treatment. For example, a church in Harper Kansas was treated for termites in July 1995 with 626 gallons of Equity (a product containing chlorpyrifos). One year later, in July 1996, chlorpyrifos was still detected in the air and it was confirmed that the product had been misapplied into the air ducts. People who worked at the church reported symptoms that were consistent with chronic neurobehavioral poisoning due to chlorpyrifos months after the treatment. Many other examples of spills and misapplications leading to measurable exposure months later could be cited. Even when chlorpyrifos is applied properly for the control of

termites, low vapor concentrations can be measured as long as eight years following treatment based on studies conducted by Wright et al. (1988, 1994).

3. Page 23 "Chlorpyrifos toxicity does not occur in the absence of significant cholinesterase inhibition. . . . It requires 10 times more chlorpyrifos to inhibit cholinesterase activity in the brain than in plasma or erythrocytes (RBC). Furthermore, toxicity is not observed until brain cholinesterase is depressed by more than 50%". While this may be true for the animal data, there are no studies measuring brain cholinesterase inhibition in humans to support these statements. Most reports of human poisonings with symptoms do not include cholinesterase tests taken at the appropriate time. There are studies of other organophosphate insecticides that suggest that human health effects (toxicity) can occur in the absence of measurable cholinesterase depression in the plasma or erythrocytes. See for example Richter et al. (1992) or Kessler and Mracek (1973). In addition, there are human data to suggest that clinical symptoms due to cholinesterase inhibition may occur in the presence of plasma inhibition but not erythrocyte or brain inhibition (Coulston et al.1972).

4. Page 28 "There is no scientific evidence that chlorpyrifos causes neurobehavioral effects." Such statements can only be made by totally disregarding the scientific literature. See Steenland et al. (1994) for evidence from human studies. In addition, the developmental neurotoxicity study in rats found that chlorpyrifos alters brain development of offspring following in utero or eary postnatal exposure (Hoberman 1998a,b) and another study reported that chlorpyrifos causes behavioral changes in both young and adult rats (Moser and Padilla 1998).

5. Page 36 "the child could accidentally ingest a 15% chlorpyrifos solution before displaying signs and symptoms consistent with exposure." The 1996 annual report of the American Association of Poison Control Centers (1997) includes the following fatality report:

> A 22 month-old boy ingested an unknown amount of an insecticide (chlorpyrifos 0.5%, petroleum distillates 0.3%, and water) which had been placed in a cup. There was immediate choking, and after ED [Emergency Department] arrival, drooling, gastric distension, and respiratory distress developed.. . . The patient remained ventilator dependent, and died due to sepsis 10 weeks after admission. Initial plasma cholinesterase value was 0.4 U/mL (normal, 8-18 U/mL). [0.4 represents 95% depression below normal.]

Two similar cases were reported by Zweiner and Ginsburg (1988) cited in the Blondell and Dobozy (1997) review where children swallowed household formulations (containing 0.5% chlorpyrifos) and experienced life-threatening effects and had very low cholinesterase values confirming poisoning by chlorpyrifos. These cases conflict with the statement by DowElanco regarding the safety of a 15% formulation, a 30 fold higher concentration.

6. Page 37 "Acutely toxic concentrations of chlorpyrifos cannot be attained following proper chlorpyrifos applications." A physician contacted EPA regarding a poisoning that occurred to his son in October 1996 in Florida. The son, who was in his 30s, mowed the hospital ground for 40 hours per week. He was often hot and sweaty while mowing and frequently removed his shirt.

On at least one occasion, the lawn had been treated with fertilizer containing chlorpyrifos in a granular or dust formulation. He reported getting considerable amounts of the material directly on his skin which he did not wash off for several hours. Though not in violation of label precautions because the label fails to list precautions about mowing after application, he did develop symptoms consistent with organophosphate poisoning. This incident strongly suggests that poisoning can occur in spite of following existing application precautions. Therefore, products intended for applications to lawns should have warnings to prevent substantial dermal contact among people other than the applicator who may experience substantial contact.

EPA has examined this critique and concluded the Dow AgroSciences review was mainly an extensive review of all the limitations of the incident data with little acknowledgment of its strengths. The above examples suggest that the review prepared by DowElanco was misleading and may contain inaccurate statements. As such, it is not a basis for revision of the Blondell and Dobozy review of 1997.

Review of "Chlorpyrifos Exposure and Human Health. Final Report of an Independent Panel of Scientists Convened by DowElanco in Cooperation with the US Environmental Protection Agency". [Epidemiology Blue Ribbon Panel Report.] October 15, 1997. (No MRID number)

A multidisplinary panel was convened by DowElanco to consider scientific evidence of the potential human health effects of chlorpyrifos. The panel consisted of eight scientists, only one of which had been recommended by EPA. Initially the panel chairman was provided with 57 studies for consideration. However, the panel chairman felt this was too many and the list was reduced to 30 studies that were subsequently sent to the panel for review. Among the studies that the panel chairman excluded were studies concerning chronic effects of organophosphates but not specific to the compound chlorpyrifos. In the opinion of the Health Effects Division, the omission of these studies and the absence of experience in the conduct of neurobehavioral epidemiologic studies of pesticides by all but one of the panel members hampered the review process and led to an unwarranted conclusion. The majority of the panel (five to three) concluded "Chlorpyrifos is a widely used and widely studied compound. The available scientific evidence provides no basis for concern that it causes human health adverse effects other than its known cholinergic effects associated with acute poisoning." Although stating the compound was "widely" studied, the majority did go on to admit that the existing literature on potential health effect was "limited". In contrast, the minority opinion (three members) stated "Chlorpyrifos is a widely used compound. There is inadequate information from epidemiologic studies to provide evidence to reach a judgment of no adverse effects resulting from levels of exposure experienced by persons engaged in the manufacture or professional application of chlorpyrifos." Note that this conclusion does not address the possibility that persons poisoned by chlorpyrifos may experience chronic adverse effects. EPA found no information in the panel report to indicate that the conclusions stated by Blondell and Dobozy (1997) needed to be changed.

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