



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 reviewed 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/m³. 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 early 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 multidisciplinary 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.

References

American Association of Poison Control Center. 1997. *American Journal of Emergency Medicine* 15(5):494.

Blondell J, Dobozy VA. 1997. Memorandum to Linda Propst, January 14, 1997. Review of Chlorpyrifos Poison Data. Health Effects Division (7509C), U.S. Environmental Protection Agency, Washington, D.C.

Coulston, F., Golberg, L., and Griffin T., 1972. Safety Evaluation of Dowco 179 in human volunteers. Institute of Experimental Pathology and Toxicology. Albany Medical College, Albany New York. March 1972. MRID No. 95175.

Ecobichon DJ. 1994. Organophosphorus Ester Insecticides. In: *Pesticides and Neurological Diseases*. Edited by Ecobichon DJ and Joy RM. CRC Press, Baton Rouge. Pages 172-249.

Hoberman, A.M. (1998a). Developmental neurotoxicity study of chlorpyrifos administered orally via gavage to Crl:CD® BR VAF/Plus® presumed pregnant rats. Argus Research Laboratories, Inc., Horsham, Pennsylvania, Laboratory study No. 302-001, Sponsor study No. K-044793-109, May 1, 1998. MRID 44556901. Unpublished.

Hoberman, A.M. (1998b). (pathology) Developmental neurotoxicity study of chlorpyrifos administered orally via gavage to Crl:CD® BR VAF/Plus® presumed pregnant rats. Argus Research Laboratories, Inc., Horsham, Pennsylvania, Laboratory study No. 302-001, Sponsor study No. K-044793-109, May 1, 1998. MRID 44661001. Unpublished.

Karalliedde L, Senanayake N. 1989. Organophosphorus insecticide poisoning. *Br. J. Anaesth.* 63:736-750.

Kessler H, Mracek JF. 1973. Nonfatal accidental organophosphate pesticide intoxication in seven inmates of a correctional institution. *Journal of the Medical Association of the State of Alabama* 42:775-781.

Litovitz TL, Smilkstein M, Felberg L, Klein-Schwartz W, Berlin R, Morgan JL. 1997. 1996 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *American Journal of Emergency Medicine* 15:447-500.

Moser V.C., and Padilla S. 1998. Age- and Gender-Related Differences in the Time Course of Behavioral and Biochemical Effects Produced by Oral Chlorpyrifos in Rats. *Tox. Appl. Pharm.* 149:107-119.

Richter ED, Kowalski M, Leventhal A. et al. 1992. Illness and excretion of organophosphate metabolites four months after household pest extermination. *Archives of Environmental Health* 47:135-138.

Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. 1994. Chronic neurological sequelae to organophosphate pesticide poisoning. *American Journal of Public Health* 84:731-736.

U.S. Congress, Office of Technology Assessment. 1990. Case Studies: Exposure to Lead, Pesticides in Agriculture, and Organic Solvents in the Workplace. In: *Neurotoxicity: Identifying and Controlling Poisons of the Nervous System*. OTA-BA-436. (Ed: U.S. Congress Office of Technology Assessment) U.S. Government Printing Office, Washington, D.C., pages 281-311.

Whitmore RW, Kelly JE, Reading PL. 1992. National Home and Garden Pesticide Use Survey Final Report, Volume I. Research Triangle Institute RTI/5100/17-01F, Research Triangle Park, North Carolina.

World Health Organization. 1990. Public Health Impact of Pesticide Used in Agriculture. World Health Organization, Geneva. 128 pages.

Wright CG, Leidy RB, Dupree HE Jr. 1988. Chlorpyrifos in the ambient air of houses treated for termites. *Bull. Environ. Contam. Toxicol.* 40:561-568.

Wright CG, Leidy RB, Dupree HE Jr. 1994. Chlorpyrifos in the air and soil of houses eight years after application for termite control. *Bull. Environ. Contam. Toxicol.* 52:131-134.

Zweiner RJ, Ginsburg CM. 1988. Organophosphate and carbamate poisoning in infants and children. *Pediatrics* 81:121-126.