Human Exposure and Risk from Indoor Use of Chlorpyrifos

James E. Gibson, Robert K. D. Peterson, and Bradley A. Shurdut

Dow AgroSciences LLC, Indianapolis, IN 46268 USA

The toxicity, exposure, and risk from chlorpyrifos are briefly discussed in juxtaposition with two recent articles in *Environmental Health Perspectives* concerning potential exposures to children. In studies conducted according to EPA guidelines, chlorpyrifos has been shown not to be mutagenic, carcinogenic, or teratogenic, nor does it adversely affect reproduction. Chlorpyrifos toxicity does not occur in the absence of significant cholinesterase inhibition. If exposures are less than those that cause significant cholinesterase depression, then no signs or symptoms related to chlorpyrifos exposure occur. The weight of empirical evidence indicates that the risk of adults or children experiencing an adverse health effect from exposure to chlorpyrifos through both nondietary and dietary sources is negligible. Both the research supporting the registration of these products and their long history of widespread use suggest that unless these products are seriously misused, their margins of safety are wide enough to protect everyone with the potential to be exposed. A weight-of-evidence review of the entire scientific knowledge base relating to chlorpyrifos products supports these conclusions. *Key words*: biomonitoring, chlorpyrifos, dislodgeable residues, exposure modeling, nondietary exposure, organophosphate insecticide, pesticide, risk. *Environ Health Perspect* 106:303–306 (1998). [Online 28 April 1998]
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The commentary by Davis and Ahmed (*1*) and the study by Gurunathan et al. (*2*) raise concerns about potential nondietary exposures of infants and children to chlorpyrifos when applied in the home. Dow AgroSciences is committed to assessing and understanding potential human exposures to all of our products, including chlorpyrifos. Consequently, although Gurunathan et al. (*2*) should be recognized for their novel effort to quantify potential multipathway exposures to children, several of their comments and conclusions, as well as statements by Davis and Ahmed (*1*), require further consideration.

Chlorpyrifos is an exceptionally well-understood and widely studied molecule. More than 250 studies have been conducted examining the uses and impacts of this molecule on human health and the environment. Indeed, to our knowledge, no other pest control product has been researched more thoroughly. Further, the scientific weight of evidence strongly supports its safety when used in the indoor environment.

Risk associated with any substance is a function of toxicity and exposure. Therefore, both toxicity and exposure for any pesticide, including chlorpyrifos, need to be determined and understood in order to make informed decisions about its proper use. To effectively and efficiently manage human and environmental health, both public policy and regulatory decisions regarding risk from any activity, including pesticide use, must be based on sound science, particularly with respect to empirical understandings of toxicity and exposure.

In this commentary, the toxicity, exposure, and risk from chlorpyrifos are briefly discussed. Additionally, the relationship between the findings of Gurunathan et al. (*2*) and current use patterns for chlorpyrifos are discussed in juxtaposition to the misconceptions and misinterpretations by Davis and Ahmed (*1*). Finally, limitations of anecdotal information and our company's product stewardship initiatives to assure proper and safe use of chlorpyrifos are discussed.

Toxicity of Chlorpyrifos

In studies conducted according to EPA guidelines, chlorpyrifos has been shown not to be mutagenic (*3*), carcinogenic (*4*), or teratogenic (*5,6*), nor does it adversely affect reproduction (*6*). Chlorpyrifos toxicity does not occur in the absence of significant cholinesterase inhibition. If exposures are less than those that cause significant cholinesterase depression, then there are no signs or symptoms related to chlorpyrifos exposure. Numerous studies have shown that inhibition of plasma cholinesterase activity is the most sensitive indicator of exposure to chlorpyrifos. However, there are no known adverse effects associated with the inhibition of plasma cholinesterase activity per se (*7*). The existing data provide convincing evidence that plasma cholinesterase activity is depressed by much lower doses of chlorpyrifos than those necessary to cause signs and symptoms. Moreover, these data show chlorpyrifos toxicity will not occur in the absence of significant inhibition of plasma cholinesterase activity.

Exposure to Chlorpyrifos

The toxicological effects of chlorpyrifos have been extensively studied. The dose response for chlorpyrifos is well known and can be used to state the likelihood of incurring an effect following an exposure of a given magnitude. Therefore, accurate empirical exposure studies are crucial to determining risk presented by chlorpyrifos. The weight of empirical evidence indicates that the risk of adults or children experiencing an adverse health effect from exposure to chlorpyrifos through both nondietary and dietary sources is negligible (*8–10*).

The objective of the Gurunathan et al. study (*2*), conducted at the Environmental and Occupational Health Sciences Institute at Rutgers University (EOHSI), was to evaluate potential exposures to children following an indoor broadcast application with chlorpyrifos. Understanding potential multipathway exposures to compounds such as chlorpyrifos is important. Therefore, in an attempt to describe potential dermal and oral exposure pathways, both plastic and plush foam-based toys, as well as horizontal surfaces throughout two treated apartments, were chemically desorbed with hexane to quantify total chlorpyrifos residues postapplication. The study investigators extrapolated human exposure estimates by linking these independent residue measurements with conservative assumptions describing potential human uptake of these residues (i.e., activity patterns, frequency of skin contact with contaminated surfaces, hand-to-mouth behavioral patterns, residue dislodgeability, and transferability from contacted surfaces to human skin). However, because biomonitoring was not conducted, the assumptions cannot be sufficiently validated.

The EOHSI researchers measured chlorpyrifos residues following an indoor broadcast treatment, a form of application that has been outdated by newer technologies and which Dow AgroSciences has agreed to withdraw voluntarily on a global basis from its product label. However, Dow AgroSciences continues to support an indoor crack and crevice and spot treatment registration for chlorpyrifos. In contrast to a broadcast application, a crack and crevice and spot application typically consists of a directed low volume application to cracks, crevices, baseboards, and other sites in a structure likely to harbor the target pests.

Address correspondence to R.K.D. Peterson, Dow AgroSciences LLC, 9330 Zionsville Road 306/2C, Indianapolis, IN 46268 USA.
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Because a small volume of a dilute chlorpyrifos mixture is applied to somewhat remote areas within a home, neither direct contact with the treated areas nor volatilization with subsequent nontarget deposition is likely. Therefore, as confirmed by extensive measurements from crack and crevice studies, both dermal and oral exposures would be negligible in contrast to a broadcast application (*10,11*).

Similar studies for broadcast use patterns incorporating environmental measurements and the quantification of chlorpyrifos' metabolite in residents' urine demonstrate the inherent conservatism of many of the assumptions included in the EOHSI study (*8*). Biological monitoring results indicate that estimated exposures for children calculated by the EOHSI investigators may overestimate actual exposures following a broadcast application by at least one order of magnitude.

The EOHSI study attempted to estimate residues using solvent extraction techniques that overestimate actual human exposures because of the affinity of chlorpyrifos to bind tightly to surface matrices (*8,10,12–14*). The study assumes that all residues present on a surface can be removed and subsequently transferred to the skin, where they are prone to either percutaneous absorption or ingestion. Chlorpyrifos residues have a high affinity for binding with surfaces following application. Only a very small fraction of a measured residue is likely to be removed when children either contact or chew on a chlorpyrifos-containing surface (carpet or toys). The assumption that all of the material desorbed from polyurethane toys is available for ingestion by a small child causes an overestimation of actual exposures. Also, solvent-extracted surfaces and toys clearly overestimate an occupant's potential exposure to residues. Comprehensive exposure studies show that less than 1% of chlorpyrifos residues typically present on a household surface may be transferred to the skin upon contact with the chlorpyrifos-containing surface (*8,10,13*) (in contrast to the 100% transfer factor assumed by the EOHSI investigators). In addition, biomonitoring of volunteers performing child-like activities following a broadcast application demonstrate that potential exposures were approximately 10 times below those presented in the EOHSI study (*8*). In this case, exposures were well below the acute NOEL (no observed effect level) of 500 µg/kg/day associated with red blood cell cholinesterase depression and therefore would not result in exposures sufficient to cause adverse health effects.

Residues sorbed into and on polyurethane toys or other sorbtive surfaces do not accurately reflect potential exposures. Substrates such as polyurethane are commonly used for the collection of airborne residues of pesticides and recommended by the EPA's Subdivision U guidelines due to a pesticide's affinity to bind tightly with the material. As in the case with routine air sampling using this matrix, a solvent is used to pull or extract the trapped chemical off this media for analysis. Incidental surface contact by moist hands or chewing (similar to chemical extraction with water or a saliva-like solvent) would not efficiently remove the bound chemical (especially chlorpyrifos) from the polyurethane, which is evidenced by the need to use a nonpolar solvent to enhance desorption efficiencies when analyzing chlorpyrifos from the monitoring medium (*15*). Therefore, a child's oral or dermal exposure is not consistent with residue levels in or on a polyurethane toy measured by solvent extraction. This, coupled with the high hand-to-mouth behavior estimated by the researchers, significantly impacts and likely overestimates the absorbed doses calculated in this study. Consequently, these results should not be used to describe potential risks to children living in a recently treated home from a crack and crevice or spot treatment. However, until these results are properly validated with biological monitoring techniques, the investigators' findings could be used to generate hypotheses for future research.

Studies using crack and crevice treatments show that potential exposures to chlorpyrifos are well within accepted health guidelines. A comprehensive residential exposure study to characterize potential total exposures to children and adults over a prolonged period following crack and crevice applications was recently completed (*15*). Environmental and biological monitoring measurements were conducted to quantify the residents' absorbed doses of chlorpyrifos and, more importantly, to describe precisely the relationship between residue measurements made in the home environment and actual bioavailability. Both measured adult and extrapolated child absorbed doses were well below those estimates presented in the EOHSI study and the relevant NOEL associated with chlorpyrifos.

The use of both hard and soft toy dosimeters in the recent study demonstrated negligible residue deposition on surfaces likely to be contacted by children (*15*). Although minimal residues were detected on cotton dosimeters (used as surrogate dosimeters to simulate nontarget deposition on household surfaces and soft toys) over the 10-day period after application, side-by-side dislodgeable residue measurements performed on carpeted surfaces and plastic toys adjacent to the cotton dosimeters showed that none of the chlorpyrifos was dislodged upon contact with these surfaces. In addition, chlorpyrifos loading on the passive cotton dosimeters was at least 400 times less than the surface loading documented in the EOHSI study for plush toys.

Therefore, in contrast to the EOHSI study in which surface residues were estimated to contribute to 99% of a child's overall exposure, dermal exposure and/or ingestion of dislodged chlorpyrifos following a crack and crevice application would not likely contribute to one's overall exposure (*15*). During a crack and crevice application or spot application, a coarse pin spray is typically directed into confined spaces that may harbor crawling pests. Because of the nature of the application, the low volume applied, and the concentration of material used (0.25%–0.5%), potential exposures are considerably less than those following a broadcast application. Several studies have been conducted to evaluate exposures to residential occupants following crack and crevice applications (*11,16*). Based on the results of these studies, even assuming that a resident was potentially exposed to the maximum concentration for a period of 24 hr, exposures would be approximately 73 and 365 times below the acute NOEL associated with depression of human plasma or red blood cell cholinesterase, respectively. In light of the large margins of safety when estimating exposures to residents following typical pesticide applications, it is extremely unlikely that, even in the case of a misapplication, exposures would be sufficient to cause a symptomatic health effect.

Moreover, as demonstrated in the more recent study (*15*), there was no discernible biological exposure to residents attributed to the crack and crevice treatments. Because of the lack of dislodgeable residues on surfaces within the home following a crack and crevice application, exposures via either the dermal or oral route would not significantly impact a person's potential exposure to chlorpyrifos.

Limitations of Anecdotal Information

Davis and Ahmed (*1*) discuss conclusions from a 1997 EPA memorandum concerning chlorpyrifos poisoning data reported from legal claims and surveillance data provided by the American Association of Poison Control Centers and the California Pesticide Illness Surveillance Program (*17*). The 1997 EPA memorandum, which based

its conclusions as to cause and effect on anecdotal, inquiry-based information, is inappropriate, particularly when considered in conjunction with the abundance of toxicological data and risk assessments available for chlorpyrifos. Further, the conclusions and recommendations of the memorandum are not even supported by the assemblage of anecdotal information contained within the memorandum itself.

In response to the EPA memorandum, Dow AgroSciences, in cooperation with the EPA, formed an eight-member multidisplinary panel of independent scientists from government and academia charged with reviewing the scientific literature on human health effects potentially associated with exposure to chlorpyrifos (*18*). The panel was asked to 1) evaluate human experience data available and address the adequacy of the current database; 2) develop a list of recommendations for potential epidemiology studies, including suitable end points and populations and pros and cons of each approach; and 3) write a report to summarize its recommendations.

The majority opinion of the panel (five of eight members) was that no further epidemiology studies were recommended for populations exposed to chlorpyrifos with respect to potential adverse effects. The majority 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.

In reaching its conclusions, the panel examined available scientific evidence on a variety of neurological, behavioral, and immunological disorders; multiple complaints; and birth defects. The panel was not persuaded after extensive review that exposure to chlorpyrifos-containing products has been shown to be a cause of any conditions described in the complaints contained in poison control center databases and cited in the EPA memo.

Davis and Ahmed (*1*) note that prenatal exposure to chlorpyrifos has been identified as a possible explanation for birth defects in children, citing Sherman (*19*). Articles by Sherman have alleged that chlorpyrifos does cause birth defects. These papers are case reports of the same four children, with medical details drawn from the author's work as a consultant in litigation (*19,20*). There is no consistency of symptoms among the children, and three of the four have been diagnosed with disorders totally unrelated to chlorpyrifos. For two of the four (a pair of siblings), a lawsuit has been voluntarily dropped due to lack of scientific support for the claim. With a third child, the author has stated under oath that the mother's exposures to chlorpyrifos happened too late in the child's development to be toxicologically significant.

Sherman's work does not adhere to general scientific standards used in medical and clinical practice (*21*). Indeed, in a recent court ruling of the U.S. District Court for the Eastern District of Arkansas, Western Division (*21*), Judge G. Thomas Eisele stated,

> I have come to the tentative conclusion that Dr. Sherman's analysis and causation opinions are not derived from any accepted scientific methodology (i.e., are not grounded in the methods and procedures of science) [and] are not scientifically valid .... My tentative view is that Dr. Sherman's case studies do nothing more scientifically than to suggest a causal relation.

Commitment to Product Stewardship

Consistent with our company's commitment to continuous label improvement and responsible product stewardship, and in recognition of recent advancements in flea control technology, Dow AgroSciences voluntarily entered into an agreement with the EPA in June 1997 on the following 10-point program: 1) to undertake epidemiological research and establish a blue-ribbon panel to provide scientific direction for study design; 2) to continue the poison control center stewardship project (University of Minnesota); 3) to withdraw from the indoor broadcast flea control market; 4) to withdraw from the indoor total release fogger market; 5) to withdraw from the paint additive market; 6) to withdraw from the direct application pet care product market (shampoos, dips, sprays); 7) to revise labels—that had not already been revised—to include appropriate retreatment intervals; 8) to focus pest control operator education and training on exposure mitigation, label improvements, and implementation of recent notices (96-6 and 96-7); 9) to take a leadership position with the pest control industry to support the EPA's development of a new notice to cover consumer "right to know" and indoor product "best management practice" label revisions (e.g., "do not apply to furniture, toys, etc,..."); and 10) to expedite implementation of a notice on termiticide labeling and pet care product labeling revision (*22*).

Dow AgroSciences has taken a leadership role in a number of areas that enable accurate evaluation and responsible use of pesticides in the urban environment. Examples of this leadership include our recent role in finalizing a notice concerning termiticide labeling, our development of a scientific methodology for estimating potential aggregate exposure to pesticides in the urban environment, and the generation of an unequaled portfolio of training materials that we have disseminated widely to industry professionals.

Conclusions

Dow AgroSciences recognizes that chlorpyrifos-containing products are used in and around 20 million American homes each year to protect families, their children, and pets from disruptive and potentially health-threatening insect pests. Both in providing these products and in its ongoing efforts in support of product stewardship, Dow AgroSciences has consistently sought to maintain the highest standards of ethics and environmental responsibility.

Extensive research and more than 30 years of use have shown that chlorpyrifos-containing products can be used safely by home owners, gardeners, pest control applicators, and others. Both the research supporting the registrations of these products and their long history of widespread use suggest that unless these products are seriously misused, their margins of safety are wide enough to protect everyone with the potential to be exposed. A weight-of-evidence review of the entire scientific knowledge base relating to chlorpyrifos products supports these conclusions.

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