Industry Testing of Toxic Pesticides on Human Subjects Concluded "No Effect," Despite the Evidence

The National Academy of Sciences (NAS) convened a panel of scientists in early 2003 to advise the U.S. Environmental Protection Agency (EPA) on the scientific and ethical issues surrounding the use of toxicologic studies conducted by third parties on human subjects (NAS 2003). These studies are generally sponsored by chemical manufacturers to provide data for setting regulatory standards or for registering chemicals for commercial use. The test substance is frequently a pesticide or industrial chemical with no medicinal value. Studies of the pesticides dichlorvos (DDVP) and aldicarb are illustrative. The sponsors' intent was to force the U.S. EPA to consider these data for setting exposure standards (Mitka 2003).

DDVP, an organophosphate pesticide, exerts its toxicity through inhibition of acetyl cholinesterase. Symptoms of poisoning include diarrhea, vomiting, salivation, convulsions, and—in extreme cases—death. DDVP is widely used in pesticide-impregnated resin strips. It is listed as a possible human carcinogen by the International Agency for Research on Cancer (IARC 1991) and a probable human carcinogen by the U.S. EPA (1994). The AMVAC Chemical Corporation submitted a report to the U.S. EPA titled *Dichlorvos: A Single Blind, Placebo Controlled, Randomized Study to Investigate the Effects of Multiple Oral Dosing on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers* (AMVAC 1997). According to the report, subjects were given 21 daily oral doses of 7 mg dichlorvos (six subjects), or placebo (three subjects). A venous blood sample was taken every 2–3 days, immediately before dosing. The authors (AMVAC 1997) reported that, compared with the group mean predose cholinesterase activity,

> The repeated measures analysis of variance [ANOVA] showed statistically significant differences from the placebo group (1% level) on days 7, 11, 14, 16, and 18.

Despite these reported effects, the study concluded that "none of these differences were considered to be of biological significance" and that "a no observed effect level was established at 7 mg dichlorvos (equivalent to approximately 0.1 mg/kg/day for a 70 kg male) …" (AMVAC 1997). The conclusion attempted to dismiss the measured effects on cholinesterase inhibition by the poorly substantiated assertion that no relevant biological consequences would be expected at this level of inhibition, whereas the only biological end point measured in the study was cholinesterase inhibition, and this was significantly inhibited.

Aldicarb, a carbamate pesticide, also exerts its toxicity through acetyl cholinesterase inhibition. Allowable levels of aldicarb on food were set by the U.S. EPA in 1977, based on data from an unpublished report by Union Carbide (Haines 1971). Union Carbide tested three groups of four healthy adult males (at 0.025, 0.05, and 0.1 mg aldicarb per kilogram body weight, with no placebo or control group), and determined that, on the basis of subclinical blood cholinesterase inhibition, 0.025 mg/kg aldicarb was the lowest dose having an effect (lowest observed effect level; LOEL). From this study the U.S. EPA set a no observed effect level (NOEL; the maximum dose having no effect) for cholinesterase inhibition of 0.01 mg/kg/day (National Research Council 1997) (Figure 1). Subsequent food poisoning incidents, however, demonstrate the danger of reliance on such studies. In 1990, Goldman et al. (1990) published a report of three aldicarb food-poisoning incidents. The LOEL was 0.0023 mg/kg, observed in a 66-year-old woman after she consumed contaminated cucumber (Figure 1). Goldman et al. (1990) reported that "within 45 minutes she experienced nausea, vomiting, sweating, dizziness, loss of balance, disorientation, and fatigue." Most estimated dosages resulting in adverse effects were well below the 0.025 mg/kg LOEL reported by Union Carbide (see study comparison in Figure 1).

Following the food-poisoning incident, Rhone-Poulenc (Lyon, France) took over the registration of aldicarb. It then sponsored a single oral dose, double-blind placebo-controlled study with human subjects (Wyld et al. 1992) using the following doses: placebo (16 males, 6 females), 0.01 mg/kg (8 males), 0.025 mg/kg (8 males, 4 females), 0.05 mg/kg (8 males, 4 females), and 0.075 mg/kg (4 males). Wyld et al. (1992) reported that red blood cell cholinesterase activity was statistically significantly depressed at all doses compared with the placebo group (repeated measures ANOVA, two-tailed, 5% significance level). Despite a total of 24 adverse events reported by subjects (localized sweating, lightheadedness, headache, salivation), the authors reported that only one event was treatment related (profuse sweating in the highest dose group). Wyld et al. (1992) reported that there were no treatment-related clinical symptoms at doses ≤ 0.05 mg/kg (the study NOEL), a dose that was severe enough to require hospitalization and atropine treatment for one person in the California food-poisoning incident (Goldman et al. 1990).

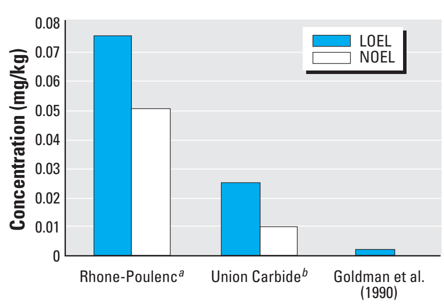

Figure 1. A comparison of the NOEL and LOEL from three separate studies of human exposure. [a]Wyld et al. (1992). [b]Haines (1971).

A study of a handful of healthy adult subjects is inadequate to determine the expected response to toxic chemical exposures from population diverse in ethnicity, life-stage, sex, health status, genetic makeup, metabolism, and nutritional status. Such studies often lack enough subjects to provide adequate statistical power to detect an effect if it is present (Bekelman et al. 2003). When studies are sponsored by chemical manufacturers with a financial interest in the study outcome, the studies may be biased in design and in interpretation. Efforts by the chemical manufacturers to foist these scientifically misleading studies on the U.S. EPA in order to weaken regulatory standards is profoundly troubling.

The authors declare they have no competing financial interests.

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Study Criticisms Unjustified

Sass and Needleman question the scientific value of data from human studies sponsored by the product's manufacturer. They also state that studies conducted by third parties on human subjects should not be considered. They base this on their disagreement with some of the interpretive statements in the "Discussion" of the AMVAC report on dichlorvos (AMVAC 1997).

We disagree with their assessment for several reasons. First, human data are recognized by regulatory agencies and the scientific community as the most relevant data for assessment of human risk of harm [International Programme on Chemical Safety (IPCS) 2002; U.S. Environmental Protection Agency (EPA) 1989, 1993, 1994, 2002, 2003; World Health Organization (WHO) 1994, 2001). Sass and Needleman do not provide any authoritative reference for the automatic dismissal of third-party human data they propose. Data from laboratory animals used in toxicologic assessments are useful, but as a large cooperative study by the pharmaceutical industry has recently shown, animal data are prone to false-negative and false-positive results, significantly limiting their ability to predict human toxicities (Olson et al. 2000).

The validity and ethicality of the data from any study are not determined by the identity of the study's sponsor, the potential uses of the material being tested, or the author's affiliation; to do so would be arbitrary and without scientific merit. Studies should be considered if they are validly designed and implemented according to scientific and ethical standards of their time. The study on dichlorvos (AMVAC 1997), cited by Sass and Needleman, was conducted in accordance with the Declaration of Helsinki, including all amendments up to and including the Hong Kong revision of 1989 (World Medical Association 2002). Further, it followed the U.K. Principles of Good Laboratory Practice (Her Majesty's Stationery Office 1999), it was performed in accordance with the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (OECD 1998) and the requirements of the European Commission (1986, 1988). The fact that the AMVAC study complied with these practices was stated in the report (AMVAC 1997), but this was not mentioned by Sass and Needleman. Both the ethics and the scientific validity are established by meeting such stringent requirements.

Sass and Needleman incorrectly state that cholinesterase inhibition was the only biological end point measured in the study (AMVAC 1997). Signs and symptoms were obtained from the individuals on a daily basis, and the study was conducted under medical supervision requiring daily visits to the laboratory by each participant. In addition, medical assessments, including clinical chemistries, hematology, blood pressure, electrocardiograms, and lung function tests, were carried out before and after the study. We are not aware of any studies that demonstrate an effect more sensitive than blood cholinesterases at very low doses of dichlorvos. Sass and Needleman do not cite any scientific study in support of their allegation that some adverse effect would have been missed at the dose tested.

It is the regulatory agencies and the scientists that work for them who evaluate study results and make regulatory conclusions based upon them, not the laboratory performing the work, the study director, or the company sponsoring the study.

The AMVAC study shows a slight effect on red blood cell (RBC) cholinesterase that develops over the course of the study with maximal mean group inhibition of 16% measured at day 18, the last day RBC cholinesterase was measured (AMVAC 1997). The first sentence of the "Discussion" (AMVAC 1997) clearly states:

> The results from this study showed that multiple oral dosing of dichlorvos (7 mg/kg, approximately 0.1 mg/kg/day) for 21 days caused some inhibition of erythrocyte cholinesterase activity.

This statement is consistent with the U.S. EPA review of the study (U.S. EPA 1998), AMVAC's interpretation of the data (AMVAC 1997), and the findings from other published studies (Funckes et al. 1963; Menz et al. 1974; Slomka and Hine 1981).

RBC cholinesterase values vary day to day, and any lower value cannot be assumed to be caused by the study chemical. In the AMVAC dichlorvos study (AMVAC 1997), before exposure began, RBC cholinesterase varied ≥ 20% day to day in the same individuals. In the controls, variability was apparent during the study; one individual had a statistically significant lower RBC cholinesterase on day 16 of the study but had not been exposed to dichlorvos.

The "Discussion" (AMVAC 1997) addressed how the slight level of RBC inhibition observed during the study might be interpreted in light of the lack of any adverse clinical findings. The conclusion did not attempt to "dismiss the results," and the interpretation regarding the biological significance of effects was undertaken in the context of international guidelines and published data on the significance of RBC cholinesterase inhibition. The WHO has stated that RBC cholinesterase inhibition < 25% is evidence of exposure but not of a hazard (WHO 1986). Similar interpretations have been published that indicate RBC cholinesterase inhibition > 30% demonstrates an adverse effect (Gallo and Lawryk 1991; Lotti 2001).

The AMVAC study (AMVAC 1997) did not attempt to determine the response from a diverse population, and no attempt was made to state this as an objective or a conclusion. However, there are published studies showing the response in a variety of patients in clinical studies conducted to evaluate the possible medicinal use of dichlorvos as a treatment for intestinal parasites (Cervoni et al. 1969; Pena Chavarria et al. 1969). These studies have not shown an unusual increase in sensitivity to the substance.

Last, regarding the criticism of the limited study size, the AMVAC study (AMVAC 1997) is only one of hundreds of health studies of dichlorvos in animals and humans. The available health data on any substance should be evaluated as a whole when conducting a risk assessment.

In summary, although the AMVAC study (AMVAC 1997) was a relatively small study, the analytical methods used for measuring both the dose of dichlorvos and RBC cholinesterase inhibition were state of the art. The data derived are valid because the study complied with good laboratory practices, good clinical practice, and ethical standards, and should be considered as a part of the available scientific information on dichlorvos.

The authors declare a competing financial interest because they are employed by or are consultants to pesticide-manufacturing companies.

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Ethical Standards of Studies Involving Human Subjects

In their letter, Sass and Needleman argue against the regulatory use of data from human subjects on both scientific and ethical grounds. The studies they evaluated were conducted in accordance with the same ethical standards that guide all studies involving human volunteers that are conducted by the federal government. Sass and Needleman claim, however, that these studies were not ethical and should not be used. We would like to address a common concern regarding the ethical conduct of these types of studies.

In a recent publication (Charnley and Patterson 2003), we reported the results of a study in which we sought to answer the question of ethical conduct of clinical pesticide testing performed since 1990 by evaluating whether those studies, performed according to good clinical practice guidelines [Food and Drug Administration (FDA) 1997]), provided volunteers with the same protections afforded volunteers in similar studies conducted by the federal government according to the ethical guidelines provided by the "Federal Policy for the Protection of Human Subjects," generally known as the "Common Rule" [Department of Health and Human Services (DHHS) 2001].

The Common Rule (DHHS 2001) was adopted by more than a dozen agencies by 1991, including the U.S. Environmental Protection Agency (EPA), the Department of Energy, the Consumer Product Safety Commission, the Department of Agriculture, the DHHS, the National Science Foundation, and other departments that conduct or fund research involving human subjects. The U.S. EPA has chosen not to make the protections of the Common Rule legally applicable to privately sponsored studies of regulated substances.

We evaluated the documentation from 15 recent human studies of 12 insecticides conducted at four clinical laboratories provided to us by the pesticide manufacturers, including those addressed by Needleman and Sass. The studies we evaluated comprised all of the oral pesticide studies submitted to the U.S. EPA since 1996 and before the U.S. EPA suspended the use of human data (along with one earlier study) for the purpose of tolerance setting. There were some cases for which we could not verify compliance with certain Common Rule elements because the documentation was unavailable; however, based on our evaluation, it is apparent that the studies we reviewed were conducted in a manner substantially consistent with the fundamental protections of the Common Rule: voluntary participation, informed consent, and review by an ethical committee or institutional review board (which would have considered and discussed any potentially "scientifically misleading" protocols).

From this subset of studies, it is evident that the general practice among the clinical testing laboratories currently employed by pesticide manufacturers is to conduct studies in accordance with the two most commonly followed ethical guidelines for human studies by nongovernmental entities, the Declaration of Helsinki (World Medical Association 2002) and the international guidelines for good clinical practice (FDA 1997). In addition, although we noted some deviations from Common Rule specifics, we found that the reviewed studies were in substantial compliance with Common Rule provisos. In the context of the concerns raised by Sass and Needleman, it is of interest to point out that good clinical practice specifies that institutional review board approval be contingent upon scientifically sound study design and purpose; the Common Rule includes no such requirement.

Standard toxicity testing protocols using laboratory rodents are considered adequate for establishing safe exposure limits for most chemicals under most conditions. Nonetheless, because rodents are not perfect human surrogates, regulatory and other organizational guidance for establishing such exposure limits give priority to results obtained from observations of humans. When human observations are unavailable, results from laboratory animals are preferred but are treated as uncertain. A recent study (Dourson et al. 2001) has suggested that, in some cases, failure to use human data in regulatory safety assessment may threaten public health because using only animal data would lead to less stringent exposure limits for some chemicals than those that would have been derived on the basis of human data. When that is the case, failure to consider ethically obtained human data for setting limits on pesticide or other chemical exposures would itself be unethical.

Perhaps some of the concerns about the ethical conduct of studies conducted by clinical laboratories for third parties and submitted to the U.S. EPA might be avoided if application of the Common Rule were extended to such studies or if the recommendation of the National Bioethics Advisory Commission for a national oversight system for all research involving human subjects were implemented. In any case, our evaluation has shown that recently conducted industry-sponsored pesticide clinical studies were conducted according to the same ethical standards adhered to by federally conducted or funded studies. Needleman and Sass's contention that those studies were conducted unethically is not supported by the available data.

The article by Charnley and Patterson (2003) was partially supported by the pesticide industry, which wanted an independent review of its studies. Because they did not receive payment for writing this letter, the authors declare they have no competing financial interests.

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Statement of CropLife America on Pesticide Testing Involving Human Subjects

As the regulatory policy leader of CropLife America, the national trade association representing the crop protection industry, I would like to respond to the letter from Sass and Needleman, which criticizes human testing of pesticides.

On 14 December 2001, the U.S. Environmental Protection Agency (EPA) commissioned the National Academy of Sciences (NAS) to examine the "scientific and ethical issues" posed by the U.S. EPA's use of human tests in registering pesticides and evaluating environmental contaminants and other chemicals in order to set safe levels of exposure. The NAS position is important because the U.S. EPA has conducted human studies on environmental contaminants and other compounds for many years and requires pesticide registrants to conduct and submit human testing data such as worker exposure, biomonitoring, and pharmacokinetic studies. The U.S. EPA has a long history of requesting and accepting industry-sponsored "third-party" human testing and using these data in its risk assessment process (U.S. EPA 1998).

Following an intense media campaign and political pressure by activist groups the U.S. EPA reversed its policy relative to industry-sponsored human testing of pesticides in December 2001, without following applicable legal requirements. In June 2003, the U.S. Court of Appeals overruled the U.S. EPA on this matter (CropLife America et al. *v.* U.S. EPA 2003), reinstating the U.S. EPA's previous practice of

> considering third-party human studies on a case-by-case basis, applying statutory requirements, the Common Rule, and high ethical standards as a guide … until it is replaced by a lawfully promulgated regulation.

In considering the scientific merits and ethical acceptability of human studies with any chemical, medicine, cosmetic, or household product, it is necessary to consider the comparative risks and benefits. Crop protection and other pest control products provide enormous societal benefits in the form of plentiful food of high nutritional quality; reduction in exposure to foodborne allergens, mycotoxins, and other natural toxins; control of human disease vectors; reduced need for agricultural land; and reduced need for manual labor.

The crop protection industry is legally and ethically bound to provide to government regulators the information they need to judge the safety of products and to set guidelines for their proper use. Likewise, the U.S. EPA is bound by law to consider all "available data" in evaluating the safety of pesticide use (Food Quality Protection Act of 1996). The vast majority of the toxicity tests conducted by industry under government guidelines use laboratory animals or *in vitro* procedures. When appropriate, human studies are conducted to confirm the relevance of animal data for humans, thus increasing confidence that the products are safe.

Human volunteer studies with pesticides are conducted under scientific and ethical guidelines equivalent to those followed in phase 1 clinical trials of potential pharmaceutical products. Phase 1 trials are also carried out in healthy volunteers who receive no direct benefit. Results of phase 1 trials are used to provide assurance that patients can be treated with safety in subsequent clinical trials for pharmaceutical efficacy. In both types of trials, pharmaceutical and pesticide, and under the required safeguards, the individual volunteers accept a small personal risk for a large societal benefit. An extensive toxicology database is available for pesticides before any human studies are even considered. This allows the use of pesticide doses that can be predicted not to cause adverse effects, thereby minimizing the risk to volunteers. These scientific points have been clearly articulated to the NAS committee examining this issue.

The Joint Meeting on Pesticide Residues (JMPR) of the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations (FAO 2002) has stated that

> Human data on a pesticide, whether from volunteer studies or from other investigations of human exposures in the workplace or environment, can be extremely valuable in placing the animal data in context and, when available, should always be evaluated even when they are not used to derive a reference dose. However, when performing a risk assessment on a pesticide, the entire database should be considered and the most appropriate studies and safety factors used to derive reference values.

The JMPR also emphasized the need to look at the scientific merit of human studies and clearly pointed out that human studies must conform to accepted international standards.

The "Common Rule" (U.S. EPA 1991) is a well-established, rigorous set of legal, regulatory, scientific, and ethical guidelines that regulates research involving human studies conducted or sponsored by federal government agencies and incorporates the principles set forth by the U.S. Food and Drug Administration, the WHO, and the World Medical Association Declaration of Helsinki (World Medical Association 2002).

The crop protection industry supports application of the Common Rule to regulate third-party human clinical trials conducted and submitted to support pesticide registrations. A thorough review shows that past studies conducted by industry met the conditions of the Common Rule, although not specifically required by regulation to do so (Charnley and Patterson 2003).

Human testing of pesticides is not intended to determine levels of exposure that cause adverse effects but rather to confirm the adequacy of established safe levels of exposure. This can be achieved in different ways, depending on the needs of the risk assessment process. For example, biochemical markers, such as enzyme inhibition in blood, might be measured instead of the effects themselves in other organs such as the brain. Such data are of immense value in establishing whether humans are more or less sensitive than animal species and help to reduce uncertainty in applying laboratory data to human exposure.

We believe that abandoning human testing, as proposed by some groups who are generally opposed to the use of pesticides and chemicals, would jeopardize public health and make it more difficult for regulators to set safe exposure levels for workers and consumers. Regulators would be faced with greater uncertainty in assessing potential risks. Using human data, we can confirm the adequacy and appropriateness of the margin of safety. Lack of appropriate data would limit the availability of a wholesome and safe food supply, as well as reduce protection from dangerous disease vectors. Above all, decades of well-considered legal, regulatory, and scientific protocols requiring human volunteers to assure the safe development of medicines should not be ignored in the safe development of pesticides.

Moreover, it would be unethical to ignore existing human data per se. The scientific validity of a study and its conformance with ethical standards applicable at the time it is conducted must be determined by objective evaluation, not by the identity of the study's sponsor, the potential uses of the material being tested, or the author's affiliation. When the weight-of-evidence approach is used, and it includes data from studies in humans, allowable levels of exposure may be either increased or decreased (Dourson et al. 2001).

The author declares he has a competing financial interest because he is employed by CropLife America, the national trade association representing the industry that manufactures and sells agricultural pesticide products. CropLife America's member companies conduct and submit to the U.S. EPA the research that supports registration of pesticide products, including the human clinical trials in question.

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Aldicarb Study Misrepresented in Human Testing Debate

The pesticide industry is legally and ethically bound to provide government regulators with the studies needed to determine that our products do not cause "unreasonable adverse effects." The scientific tests we conduct under government guidelines use laboratory animals almost exclusively. In fact, human studies are not conducted until we have a good understanding of safe levels of human exposure based on animal testing. When appropriate, human studies are conducted to confirm the relevance of animal data and ultimately increase confidence in the overall safety assessment. When performed ethically and scientifically, there is no substitute for the knowledge gained from these studies.

In their letter, Sass and Needleman state that human volunteer studies conducted with pesticides are scientifically misleading and are foisted on the U.S. Environmental Protection Agency (EPA) in order to weaken regulatory standards. They cite the aldicarb human studies as one of the examples supporting their position. Bayer CropScience takes issue with their misrepresentation of the extensive aldicarb database.

It is known that aldicarb can cause inhibition of cholinesterase, a well-known biomarker of exposure. In fact, all of the animal and human cholinesterase data generated over the last 40 years support a no observed effect level (NOEL) of 0.01–0.025 mg/kg body weight (bw). The U.S. EPA has relied on this data to set the reference dose (RfD) and to assess risk to humans.

Between 1985 and 1988, three separate incidents of alleged human foodborne poisoning from illegal applications of aldicarb to watermelons and cucumbers occurred in California (California EPA 1989) and were reported by Goldman et al. (1990a, 1990b). The authors attempted to derive exposure estimates for these alleged aldicarb incidents from average body weights, self-reports of symptoms and consumption, and average aldicarb residues from those watermelons and cucumbers that were available for analysis. Specifically, the authors' questionable derivation of high consumption levels deliberately biased toxicity estimates. The description of cases used for estimates was very limited in terms of onset, duration, and severity. Many of the symptoms of cholinesterase inhibition were nonspecific and difficult to diagnose in the onset of illness.

In 1991, the U.S. EPA considered that the incident data were not consistent with results from a human study conducted in 1971 and that they indicated that the animal studies might not be predictive of the human response. Thus the agency revised the RfD from 0.001 to 0.0002 mg/kg bw/day.

Following the U.S. EPA's decision to revise the RfD, the New England Epidemiology Institute (Rothman et al. 1991) reviewed the articles by Goldman et al. (1990a, 1990b) and concluded that they "… form an inappropriate foundation for establishing a reference dose."

Taking into account these events, Bayer CropScience concluded that reliable human data would be necessary to refine the dose response and time course of cholinesterase inhibition following exposure to aldicarb and to further investigate the relative sensitivity of humans compared to animals.

The 1992 aldicarb human volunteer (double blind) study was conducted at Inveresk Clinical Laboratories in Edinburgh, Scotland (Wyld et al. 1992) according to all of the recommended scientific and ethical guidelines that were in place at the time of the study. Inveresk is a well known experimental laboratory experienced in conducting both human and animal studies. Before the study was initiated, the Ethics Review Board of Inveresk Clinical Laboratories approved the study design and objectives. The candidates were all prescreened and given physical examinations. Their personal physicians were also consulted for any medical reasons that might preclude an individual's participation in the study. Information sheets on the profile of aldicarb were given and explained to the candidates. Informed consent forms were then given to and signed by all study participants.

No serious adverse effects occurred in this study. One male subject (0.075 mg/kg bw group) developed profuse sweating, which was reported to be related to aldicarb. Of the remaining 23 symptoms reported, almost half were noted in the placebo group (22 individuals), whereas the others were either not related to the expected time course of symptoms, not consistent with symptoms associated with cholinesterase inhibition, or were noted among the remaining 35 individuals. Thus, the NOEL for clinical symptoms was 0.05 mg/kg bw and the NOEL based on inhibition of RBC was 0.025 mg/kg bw (Figure 1).

In 1992, Bayer CropScience submitted the human volunteer study (Wyld et al. 1992) to the U.S. EPA. The agency reviewed the aldicarb human study and determined that it was acceptable and that it was a key study to set the RfD (U.S. EPA 1992). The U.S. EPA determined the overall NOEL in this study to be 0.01 mg/kg bw/day, confirming the NOEL established in multiple animal studies. The RfD was reestablished at 0.001 mg/kg bw/day. The U.S. EPA has used this RfD to assess risk since 1992. In addition, the agency also had the study reviewed by a Joint Science Advisory Panel/Science Advisory Board in 1992 (U.S. EPA 1992) and they also determined the study to be acceptable and appropriate for use in the risk assessment process. The 1998 U.S. EPA panel reaffirmed the use of the data in the risk assessment process. Also, the panel addressed additional questions or other matters concerning aldicarb. These critical facts have been omitted by Sass and Needleman and lead the reader to draw conclusions that the human study was never reviewed and accepted by the U.S. EPA and its joint advisory panels.

In conclusion, good science and the law (Federal Food, Drug, and Cosmetic Act 1997; Federal Inssecticide, Fungicide and

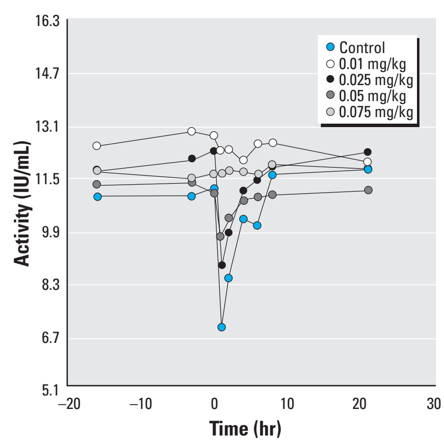

Figure 1. Time course of mean red blood cell cholinesterase inhibition after aldicarb exposure.

Rodenticide Act 1972; Food Quality protections Act of 1996) require the U.S. EPA to consider all credible data when making regulatory decisions. The aldicarb human study conducted in 1992 (Wyld et al. 1992) was essential in confirming the relevance of the existing animal database and refining the risk assessment. The weight given to any particular study or data set (human or animal) can vary depending on its scientific merit, but no valid study or data set should be discounted from the evaluation process on the basis of personal and emotional arguments.

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Clarification

Readers of the February Spheres of Influence article ("Does Secrecy Equal Security? Limiting Access to Environmental Information," *EHP* 112:A104–A107 (2004)] may have inferred that at the time Christopher Gozdor represented the Aberdeen citizens group, he was working for his present employer, the University of Maryland Center for Health and Homeland Security. In fact, Gozdor was a student attorney with the university's Environmental Law Clinic at the time he represented the group.