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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

8-13-92

**MEMORANDUM**

SUBJECT: Review of "The Epidemiology of Aldicarb Exposure in Humans: A Critique of the Literature with Emphasis on its Application to Risk Assessment"

FROM: Ruth H. Allen, Ph.D., M.P.H, Section Head (Acting)
Special Review Section
Chemical Coordination Branch
Health Effects Division (H-7509-C)

TO: William Sette, Ph.D.
Aldicarb Chemical Manager
Science Analysis Branch (H-7509-C)

THRU: Esther Saito, Chief (Acting)
Chemical Coordination Branch
Health Effects Division (H-7509-C)

Per your request, I have reviewed the critique of the above title dated June 19, 1992 prepared by P. Cole et al. The mass hysteria argument was discussed in my previous review, and need not be repeated here. While there are a number of points raised in the critique of the four published epidemiology studies, some of which have merit, I do not believe they invalidate the dosage estimates.

Given wide variability in health status, food consumption patterns, and biological diversity in humans, it is reasonable to see effects over a range of doses as estimated in different lab studies and by different analytical techniques. Plotting the pattern of doses and effects from different studies, and given the continuing reports of human poisonings from aldicarb in watermelons and cucumbers both suggest to me that something is very wrong in the way this chemical is used or misused. We can discuss this in more detail when I return in two weeks.

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2

RHÔNE-POULENC

RHÔNE-POULENC AG COMPANY

June 23, 1992

Sepehr Haddad
Office or Pesticide Programs
Document Processing Desk (SRVW 0140-Aldicarb)
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

Dear Mr. Haddad:

Attached is a recently completed report authored by Dr. P. Cole, Dr. H. Pastides and Dr. K. Rothman which reviews four papers reporting on historical incidences of illegal use of aldicarb on watermelons and cucumbers. Rhone-Poulenc commissioned this review to determine the scientific validity of the epidemiologic conclusions in the respective reports.

The conclusions of Cole et. al. were that: (1) the studies reviewed failed to account for cases that were not aldicarb related, (2) there was an absence of reliable information on the dose of aldicarb ingested, if any; and, (3) actual measurements of the amount of cucumber or watermelon consumed and the weight of the subjects involved in these cases were "imprecise".

Furthermore, the authors concluded that publicity about the incidences caused a number of people to report symptoms which were psychogenic in origin and not related to aldicarb exposure.

Rhone-Poulenç continues to believe that the most reliable data upon which to base the Reference Dose (RfD) are the human volunteer studies that are currently available for aldicarb.

Sincerely,

Warren A. Davis

Warren A. Davis
Senior Registration Manager

cc: M. Stasikowski, EPA/OW

3

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TRANSMITTAL BIBLIOGRAPHY

1. Cole, P., Pastides, H., and K.J. Rothman. The Epidemiology of Aldicarb Exposure in Humans: A Critique of the Literature with Emphasis on its Application to Risk Assessment. June 19, 1992.

4

Statement of No Data Confidentiality Claim

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10 (d)1(A), (B), or (C).

Company: Rhone Poulenc

Company Agent: W. A. DAVIS

Title: REGISTRATION MANAGER

Signature: Warren A. Davis

Date: 6/23/92

5

# Executive Summary

Aldicarb, a pesticide with anticholinesterase effects in humans, is toxic at high doses, but a threshold for toxicity has not been clearly established. In 1971 Haines[1] reported that the lowest dose of aldicarb capable of provoking an anti-cholinesterase response was 0.025 mg/kg of body weight, based on studies of human volunteers. Clinical signs of overexposure were not observed at doses of 0.05mg/kg or lower and acute symptoms were observed only in subjects exposed to a dose of 0.1mg/kg or higher.

This document provides a critical evaluation of the literature on the epidemiology of aldicarb exposure, as well as of a paper that uses data from some of the reported outbreak investigations to contribute to a quantitative risk assessment. Four published papers have reported outbreaks of symptoms compatible with cholinesterase inhibition that could have resulted from the ingestion of aldicarb. The first reported two alleged outbreaks in Nebraska associated with consumption of hydroponically-grown cucumbers. The second reported an outbreak associated with English cucumbers in the Vancouver area. The third and fourth report a large outbreak associated with watermelon consumption in Oregon and California.

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1 Haines RG: Ingestion of aldicarb by human volunteers: a controlled study of the effects of aldicarb on man. Union Carbide Agricultural products Co, Inc. Report (Unpublished).

I. Review of the Epidemiology of Aldicarb-Related Illness

TITLE: Suspected foodborne carbamate pesticide intoxications associated with ingestion of hydroponic cucumbers.

AUTHORS: E.A. Goes, E.P. Savage, G. Gibbons, M. Aaronson, S.A. Ford, H.W. Wheeler

PUBLISHED: Am. J .Epidemiol. 111:254-260, 1980

This is a report of two outbreaks of a hypothesized foodborne illness in two adjacent cities in Nebraska in April 1977 and July 1978 (one city involved each year). In the first episode, 9 residents of one town became ill 0.25 to 2.25 hours following ingestion of hydroponically-grown cucumbers. Illness lasted 4-12 hours and no specific medical treatment was given. No aldicarb was found at the greenhouse where the cucumbers were grown. Initial chemical analyses of cucumbers focused on organophosphates rather than carbamates. Later, analyses of some cucumbers procured from ill individuals indicated that " . . . a carbamate was present .. . ." but neither the compound nor its level could be determined. No assay was conducted of any material from the greenhouse that supplied the cucumbers.

The second outbreak involved 5 persons who ate cucumbers grown at the same greenhouse as those involved in the first outbreak. Illness occurred 30-60 minutes after ingestion of a cucumber and lasted 3.5-5.5 hours. It is stated that "The carbamate pesticide aldicarb was identified in many of the samples (of cucumbers obtained at the supermarket where the ill people had bought theirs) that were analyzed" but only four specific values are given. These are 0, 9.9, 6.6 and 10.7 ppm. In addition, although no aldicarb-containing products was found anywhere at the greenhouse, 1.8 ppm was

TITLE: Report of illnesses caused by aldicarb-contaminated cucumbers.

AUTHORS: G.H. Hirsch, B.T. Mori, G.B. Morgan, P.R. Bennett and B.C.Williams

PUBLISHED: Food Additives and Contaminants, 1988, M 5 (No. 2): 155-160

This article states that there were "over 300 reports of illness, mainly in the greater Vancouver area . . ." that occurred over an approximate 5 week period (29 May to sometime in June 1985). The 300 reports related to an unknown number of people but, "A review of the symptoms, time of onset of illness and food consumed indicated that at least 84 reports involving 140 people were related to the consumption of fresh greenhouse-grown long English cucumbers contaminated with aldicarb". It is also stated that the British Columbia Poison Control Center received . . . 500 calls over a two week period. Furthermore, approximately 275 calls were " also received" by the Health Protection Branch. The exact number of reports, and persons ill, is confusing and it is not possible to determine if the 275 calls are a subset of the 500 or how, if at all, either number relates to the originally mentioned "over 300 reports."

It is stated that "Initially all samples (of cucumbers) were analyzed ..." We are not told, however, whether this refers to a sample from every report or an analysis of all available cucumbers. If the latter assumption is true we are limited by not knowing how many such cucumbers there were or how, or from whom, they were obtained. Importantly, it is stated that as a result of the screening analyses, "Only the presence of aldicarb residues correlated

8

as little as 0.006 mg/kg body weight can produce symptoms. This suggestion is untenable, however, for the following reasons: First, there is no basis for knowing how many people actually were ill with cholinesterase-inhibition symptoms. It is not affirmed that any individual was seen at a hospital or by a physician. There is no information provided on the level of publicity given to the early reports. Thus, the size and severity of the "epidemic" are, in fact, unknown. Second, it is entirely unclear how the conclusion was reached that 84 reports involving 140 people were related to consumption of aldicarb-contaminated cucumbers. Quite remarkable is the authors' statement: " . . . it is evident that typical symptoms of acute carbamate poisoning were caused by aldicarb residue intakes in the range of 0.01 to 0.03 mg/kg body weight (Anon. 1980)." This statement is bizarre because the reference appeared five years before the current episode. The reference may be a typographical error, as it also appears at the end of the immediately subsequent sentence.

Third, the episode relating to adolescents is odd. Apparently, these children drank some vegetable juice made from cucumbers, carrots and tomatoes. All eight of those who drank the juice became ill within 30 minutes. Table 1 indicates that these children consumed 1 cucumber per person (or, more likely, the juice from same), yet there was a residue for analysis. Table 1 suggests that each child ingested about 0.28 mg of aldicarb residue when, in fact, the actual intake must have been less because, presumably, not all the aldicarb in a cucumber finds its way into the juice. If so, the illness-causing dose was less than 0.006 mg/kg body weight; this is unlikely in the extreme. Yet, these children (and all the subjects in Table 1) are a small sample of a large number of people who presumably became ill -

assessment provided in this published report.

reported, but having differing levels of sensitivity and specificity. Of these: 52 (19.6%) met the more stringent case definition "A" (more specific but less sensitive); nine (3.4%) met the less specific/more sensitive definition "B" (any two described symptoms plus having consumed watermelon associated with a person in the "A" group). This case definition included the requirement of a known exposure to the alleged source of illness; therefore, by definition all illness in this group would be associated with watermelon consumption, regardless of whether this was the origin of their illness or not. Forty-three (16.2%) individuals were classified as group "C"; this classification was the least specific/most sensitive and included those who reported any two symptoms.

The largest part of the purported outbreak followed the public advisory. The authors report results of laboratory analyses performed on selected watermelons alleged to have caused illness. Testing was not done on watermelons selected through a scientific sampling procedure but, instead, was performed on whatever samples were available; included were some watermelons tested "upon the request of persons reporting illness." Of 31 watermelons tested, only 16 were associated with individuals who met any case definition. Of these 16, 10 were positive for aldicarb. As a possible explanation for why six of the watermelons associated with illness did not test positive, the authors speculate that the liquid chromatography method may have been too insensitive or that watermelon component may interfere with the assay. This, of course, could have been tested experimentally using fortified samples of watermelon. It is not possible from data provided in the article to determine the results of watermelon analyses for samples eaten by those meeting case definition "A" only (fewest

TITLE: Pesticide food poisoning from contaminated watermelons in California, 1985.

AUTHORS: Goldman LR, Smith DF, Neutra RR, et al.

PUBLISHED: Arch. Env. Health 45:229-236, 1990

This paper reports an investigation of an alleged watermelon-borne epidemic that became apparent in California on July 3, 1985; it is part of the same outbreak reported by Green et al. and reviewed above. The Oregon Department of Health reported to California health authorities that aldicarb sulfoxide had been detected in "several of the melons related to illness episodes in that state." Relatively intensive case finding techniques subsequently identified 12 presumed cases of pesticide poisoning in California and large-scale, statewide advisories led to the reporting of over 600 more alleged cases during the next several weeks. Case definitions separated the reported illnesses into "probable," "possible," and "unlikely" categories based on their nature, severity, their temporal relationship with watermelon ingestion, and the number of people who became ill from eating the same melon. Simpler, but less precise, case definitions were subsequently employed. Seventeen of the roughly 1300 total suspected cases required hospitalization.

Laboratory analyses for aldicarb and aldicarb sulfoxide were performed by the state laboratory and, occasionally, confirmed by US FDA and other labs. The stated minimum detection level ranged between 0.1 and 0.5 ppm for most analyses; the minimum detection level was 10 ppb for

affected cases, 53 of the 62 melons tested contained no aldicarb. Thus, even among the probable cases, it is likely that few of those reporting symptoms were actually exposed to aldicarb. We can also infer from this observation that even among the few symptomatic individuals who were indeed exposed to aldicarb, an unknown but possibly large proportion of the cases were not caused by the aldicarb exposure.

In addition to the incidental cases in the total, it is quite plausible that the publicity stemming from the actions of the California Department of Health Services may have been responsible for many of the reported cases. Mass hysteria is a well-recognized phenomenon.[1,2,3] It has also been documented that investigating public-health officials can cause such epidemics.[4] One writer on psychogenic illness warns "don't rule out mass psychogenic illness just because a physical agent is present."[5]

Hysteria is more common among women than men, and among adolescents than among older individuals. We note from the gender and age distribution of the 17 probable cases whose melons tested positive for aldicarb (these are the only cases for which we have any information about

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1 Cole TB, Chorba TL, and Horan JM: Patterns of transmission of epidemic hysteria in a school. Epidemiol 1990;1:212-218.
2 Small GW, and Borus JF: Outbreak of illness in a school chorus: toxic poisoning or mass hysteria? N Engl J Med 1983;308:632-635.
3 Hall EM, Johnson JV: A case study of stress and mass psychogenic illness in industrial workers. J Occupat Med 1989;31:243-250.
4 Gann PH: Truth or consequences: when the study reintroduces the disease agent. Epidemiol 1990;1:192-194.
5 Singer J: Yes, Virginia, there really is a mass psychogenic illness, in Colligan M, Pennebaker J, Murphy L (eds): *Mass Psychogenic Illness: A Social Psychological Analysis*. Hillsdale, N.J. Lawrence Earlbaum Associates, 1982 (cited by Hall and Johnson, *op. cit.*)

Further evidence for the lack of a biological connection between the aldicarb content of the melons and the symptoms of the cases is the continuation of case reports after all the melons in the food distribution chain were destroyed. Among those melons purchased and eaten by "cases" after the embargo, only one melon out of 188 tested was contaminated with aldicarb. Thus, case reports did not drop off with time nearly as sharply as did the prevalence of contaminated melons.

The authors provide only cursory attention to the problem of coincidental occurrences. They state that "It has been asserted that the entire epidemic was created by media coverage and reporting of illness coincidental with eating aldicarb contaminated watermelons." However, they then reject the possibility that the entire epidemic was spurious by noting that "those with laboratory positive watermelons were likely to have a greater number and more severe acetyl cholinesterase inhibition symptoms than others." After defeating the straw man that there were no aldicarb-caused cases, the authors ignore a realistic alternative, namely that some, even if not all, of the cases were not caused by aldicarb. They go on to attribute intoxication effects to whatever aldicarb doses could be estimated among cases with exposure, oblivious to the fact that the majority of their case series may have consisted of individuals whose symptoms were unrelated to watermelon eating.

It is also possible that some level of under-reporting may have occurred; that is, some persons with watermelon-related illness were never identified by health authorities. Under-reporting is more likely for individuals with milder symptoms and for those who are not prone to

## II. Critical Evaluation of Paper Providing Toxicity Estimates

TITLE: Aldicarb food poisonings in California, 1985-1988: toxicity estimates for humans.

AUTHORS: LR Goldman, M. Beller, R.J. Jackson

PUBLISHED: Arch. Env. Health 45:141-147, 1990

This paper attempts to derive estimates of the lowest doses that cause symptoms of aldicarb intoxication. The estimates are based on three outbreaks of illness consisting of symptoms that resemble carbamate intoxication. The doses estimated were in the range from 0.0011 mg/kg body weight to 0.06 mg/kg body weight. Most of the estimates were considerably below 0.025 mg/kg of body weight, the level that had previously been accepted as the lowest level capable of causing an anti-cholinesterase response in humans, based on studies of human volunteers.

Insofar as the paper by Goldman et al. is used to estimate threshold doses for the effects of aldicarb, it embodies a fundamental flaw. The flaw is a methodologic error that would bias the estimated doses in the negative direction, that is, it would lead to estimated threshold doses that are too low. In addition, inasmuch as all the doses had to be estimated based on guesswork involving the amount of food consumed, the dose estimates are statistically unreliable compared with studies measuring the doses ingested by volunteers.

To explain the cases with no detectable exposure, the authors argue that "Although some of these could have been coincidental occurrences as mentioned above, it is also possible that the laboratory analysis was too insensitive to detect ASO at levels which cause illness." This argument is circular and not scientifically testable; if any and every exposure to aldicarb, measurable or not, in a symptomatic individual is judged to be a causal exposure, then as little as one molecule of aldicarb ultimately will be the amount deemed sufficient to cause the effect.

In addition to this fundamental conceptual flaw in the paper, Goldman et al. base their estimated doses on unreliable information. Weight, a key variable used in the dose estimation, was actually unknown; the authors relied on population averages for people of the same age and sex. Furthermore, the amount of food consumed had to be estimated retrospectively.

The data of Goldman et al. also provide evidence against the theory that children are particularly sensitive to aldicarb intoxication. We assume that the frequency of watermelon consumption among children is not much less than that of adults; our suspicion is that the prevalence of watermelon eaters among children is greater than among adults. If this assumption is correct, then the age distribution of the 17 exposed "cases" reported by Goldman et al. indicates that children are underrepresented among the cases, since only four of the 17 were under age 20, and none was under age 10. If children were especially sensitive to aldicarb intoxication, however, children should be over represented rather than underrepresented among the cases.

## Summary

This document has provided a critical evaluation of the literature on the epidemiology of aldicarb exposure. Substantial problems have been identified which seriously limit the use of data from the published outbreak investigations for the purpose of estimating the human toxicity of aldicarb.

In aggregate, the four published outbreak investigation papers have the following important limitations: the failure to recognize or account for the reported cases that were not caused by aldicarb; the absence of reliable information on the dose of aldicarb ingested; imprecise measurements of the quantity of food consumed by persons who became ill; and imprecise estimation of the weight of the subjects.

In 1971 Haines reported that the lowest dose of aldicarb capable of provoking an anti-cholinesterase response was 0.025 mg/kg of body weight, based on studies of human volunteers. Clinical signs of overexposure were not observed at doses of 0.05 mg/kg or lower and acute symptoms were observed only in subjects exposed to a dose of 0.1 mg/kg or higher. The data of Haines collected from healthy volunteers is much stronger, from a methodologic perspective and, therefore, should be given greater weight as a guide to estimating the risks of aldicarb exposure to human health. Until new epidemiologic evidence, which has accounted for the serious limitations cited above, is presented there is no reason to supplant the volunteer study as the basis for aldicarb risk assessment.



17