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Supplement to Document# 010451-DER for Case Reports of Human Exposure Paper. This supplement provides a new Executive Summary and appendices to upgrade the original DER.

EPA Reviewer: William F. Sette, Ph.D. William F Sette 1-25-99
Science Analysis Branch, Health Effects Division (7509C)

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DATA EVALUATION RECORD

STUDY TYPE: Case Reports of Human Exposure
OPPTS Number: None OPP Guideline Number: None

PC CODE: 098301 TOX CHEM Number: 011A

TEST MATERIAL: Aldicarb technical

CHEMICAL NAME: 2-methyl-2-(methylthio)proprionaldehyde-0-(methylcarbamoyl) oxime.

CITATION: Aldicarb Food Poisonings in California-1985-1988; Toxicity Estimates for Humans. Goldman, LR, Beiler M, and Jackson R. Unpublished draft, June 1990.

SPONSOR: Environmental Epidemiology and Toxicology Section, California Department of Health Services, 5900 Hollis St., Suite E, Emeryville, CA 94608

EXECUTIVE SUMMARY: In this review of case studies from a series of episodes of food poisoning attributed to aldicarb, dosage estimates from 28 cases were derived from age- and sex-average body weights, self reports of consumption and symptoms, and aldicarb sulfoxide residues from watermelon and cucumbers. This yielded a range of 0.002 - 0.0086 mg/kg for clinical signs and symptoms.
These dosage estimates are regarded as valid and reasonable estimates and the weight of the evidence presented here suggest that clinical signs or symptoms may occur in humans after acute exposure at as little as 0.002 mg/kg.

Points of clarifications for the original DER

The reference to Table 4 refers to the 1990 paper of Goldman, Smith, et al. 1990.
The dosage units on page 5 of the DER are reported as mg/kg.

Appendices

Appended to this executive summary are:

the text of the Blondell memo referenced in the DER,

the final publications referenced in the DER as draft about the first episode in California: Goldman et al., 1990;

and the final publication referenced in the DER as draft of the dosage estimates for all four episodes: Goldman, Beller, and Jackson, 1990.

DER #13

Chemical Name: Aldicarb 098301
Study Type: Case Reports of Human Exposure
Sponsor Name: N/A Year of Study 1990
MRID No. N/A
HED Doc. No. 010451

3329

Reviewed by: William F.Sette, Ph.D. William F. Sette 7/24/90
Science Analysis and Coordination Branch
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Secondary reviewer:

010451

DATA EVALUATION REPORT

STUDY TYPE: Case Reports of Acute Human Exposures

TOX. CHEM NO: 011A

TEST MATERIAL: Aldicarb

SYNONYMS: Temik, 2-methyl-2-(methylthio) proprionaldehyde O(methylcarbamoyl)oxime

STUDY NUMBER: N/A

SPONSOR: Environmental Epidemiology and Toxicology Section, California Department of Health Services, 5900 Hollis St., Suite E, Emeryville, CA 94608

SITE OF INCIDENTS: California, Oregon, Nebraska

TITLE OF REPORT: Aldicarb Food Poisonings in California - 1985-1988: Toxicity Estimates for Humans

AUTHOR(S): Lynn R. Goldman, M.D., Michael Beiler, M.D., and Richard Jackson, M.D.

REPORT ISSUED: Unpublished draft, June 1990

CONCLUSIONS:

Dosage estimates from 28 cases of alleged aldicarb poisoning were derived from age- and sex- average body weights, self reports of consumption and symptoms, and aldicarb sulfoxide residues from watermelon and cucumbers. This yielded a range of 0.002-0.0086 mg/Kg for clinical signs and symptoms.

These dosage estimates are regarded as valid and reasonable estimates and the weight of the evidence presented here suggest that effects may occur at as little as 2 ug/Kg.

B. STUDY DESIGN

The authors reviewed the available data from four reported episodes of alleged Aldicarb poisoning through ingestion of contaminated watermelons and cucumbers. Based on measurements of aldicarb sulfoxide found in some commodities of those taken ill, dosage estimates were derived from self-reports of consumption and age and sex average body weights.

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C. METHODS AND RESULTS:

Case Definitions:

Outbreak 1: California, 1985, Watermelons

Case Definitions: probable, possible, and unlikely by a complex scheme. A Probable case was defined as: Melon positive for aldicarb or metabolites
OR
Onset 2 or fewer hours after consuming melons
AND
Multiple groups of cholinergic symptoms or a single group of symptoms and more than one person ill from the same melon;
OR
Onset between 2-12 hours after consuming melon, multiple symptoms, and more than one person ill from the same melon.

J. Blondell has reviewed this study and noted that "most subjects experienced abdominal pain, nausea/vomiting, or diarrhea regardless of whether they were categorized as probable, possible or unlikely cases of aldicarb-induced poisoning. Using a case definition involving just these 3 symptoms, [diarrhea or nausea/vomiting within 2 hours of ingestion] the authors calculate a sensitivity rate (true positives) and specificity rate (true negatives) of about 80% each." He also notes the authors's admission that due to the flood of calls, not all symptoms may have been recorded for all cases. He further noted that the complete description of signs and symptoms, their onset and duration, and other details for those of whom dosage estimates were made, was not presented.

Most people had short term illnesses that resolved quickly. However, some were more seriously affected; 17 people, out of the roughly 1300 cases reported, required hospitalization. A greater proportion of "probable" cases occurred after July 11 (57 vs. 49%), suggesting to the authors a potential reporting bias after the first media report of the epidemic. However, those cases with detected residues of aldicarb sulfoxide had a greater number and more severe symptoms than cases in other categories (Table 4).

Outbreak 2: California, 1987, Watermelons

Case Definition: nausea, vomiting, and/or diarrhea in < 2 hours, probable; 2<x<4 hours, possible; and > 4 hours, unlikely, based on a sensitivity of 79% based on 1,000 cases in 1985 California episode and 4 hours because only one positive watermelon case had signs starting after this time.

Outbreak 3: California, 1988, English Cucumbers
Case Definition: same as Outbreak 2.

Outbreak 4: Nebraska, 1978, Pandex Cucumbers

Case Definition not described.

Laboratory Analyses

Samples of melons and cucumbers were requested from probable cases, and wrapped in aluminum foil and frozen until analysis. The California Department of Food and Agriculture performed analyses of Aldicarb and metabolites in the watermelons and cucumbers. For outbreak 1, there were several confirmatory analyses by either the FDA or the California Department of Health Services.

The CDFA and FDA used liquid chromatography with post-column derivatization using ortho-phthaldehyde and fluorometric detection of derivatives. The confirmatory analyses by CDHS used gas chromotography and a method of Union Carbide for analyzing aldicarb residues in water(ALDICARB-FPD-WATER; 3/80).

Minimum detection levels were between 0.1 and 0.5 ppm, depending on the laboratory and the year of the test.

Dosages were calculated based solely on the concentrations of Aldicarb Sulfoxide.

The methods reported here were reviewed by Dr. Joel Garbus of the Dietary Exposure Branch. His analysis is presented below.

"The drafts of the journal articles [this study and the article on the 1985 watermelon episode] present no grounds for questioning either the validity of the method that the California Department of Health used in determining the level of aldicarb residues in watermelons or the results. A standard method was employed that has been validated and used successfully by the FDA, the registrant, and other health departments faced with similar incidents of aldicarb associated illnesses. Further, Rhone-Poulenc has stated that one of its toxicologists assisted Californiain its analyses of the watermelons."

" What is of note is 0.2 ppm as the value for the minimum level of detection for aldicarb metabolites. This value is relatively high compared to the l.o.d. reported by the registrant (0.02 ppm) and by other laboratories (0.01 to 0.02 ppm). However, this does not invalidate the results. It does mean that watermelons that could possibly contain aldicarb at levels of less than 0.02 ppm were not detected and not considered as positive for the presence of aldicarb and therefore were not associated with symptoms of aldicarb ingestion."

" The argument that aldicarb residues would substantially degrade during the interval of collection and analysis is not supported by what is known about the stability of aldicarb in ground water and in plants. Aldicarb has been shown to be stable for a considerable time in these environments."

Dosage Calculations

Age and sex average body weights were used for body weight. Self reports were used to derive consumption estimates. They reported that the edible portion of an average watermelon weighs 16 pounds (7300 g). a semicircular slice was estimated (and confirmed by measurement) at 454 g.[1/16]

Average cucumber: 235 g (mean of 300g for large and 170g for small), and not peeled.

Dosages of aldicarb sulfoxide were compared with Aldicarb NOEL and LOEL.

Results

I independently calculated these dosage estimates for the data given; my calculated dose are given first with their numbers in parentheses.

Outbreak 1: ASO concentrations for 6 watermelons: self-reports of amount consumed, and average weights for sex and age, dosages estimated for 17 of 19 eating those 6 melons, with the other 2 giving incomplete information on amount consumed.
For Outbreak 2, in 1987, one watermelon containing 0.3 ppm of ASO was involved.

For Outbreak 3, for 2 probable cases, ASO was found, out of samples available for 11 cases; for a 12th case, a store sample was taken.

For Outbreak 4, the dosage estimates are given as ranges, because they were based on store and warehouse cucumbers, because those the patients ate had been entirely consumed.

Figure 1 is a frequency histogram of the dosage estimates from all four episodes. There are 2 modes in the distribution, one between 2-5 ug/Kg and one around 25 ug/Kg. The other remarkable feature of this distribution is that effects were seen over a roughly 30 fold range, roughly 3x the standard factor of 10 used for generic estimates of variation in population sensitivity.

Outbreak 1

1	0.027
2	0.040
3	0.026
4	0.060
5	0.024
6	0.012
7	0.048 (0.030)
8	0.086 (0.054)
9	0.038
10	0.029
11	0.029
12	0.059
13	0.024 (0.015)
14	0.0021
15	0.0026
16	0.0034
17	0.0032

Outbreak 2

1	0.0039 (0.0020)
2	0.0048
3	0.0033 (0.0017)
4	0.0052 (0.0011)

Outbreak 3

1	0.0023
2	0.012-0.025 (0.0074) mean 0.019

Outbreak 4

1	0.022-0.036, mean 0.029
2	0.035-0.057 mean 0.046
3	0.027-0.044 mean 0.036
4	0.020-0.033 mean 0.027
5	0.006-0.009 mean 0.008

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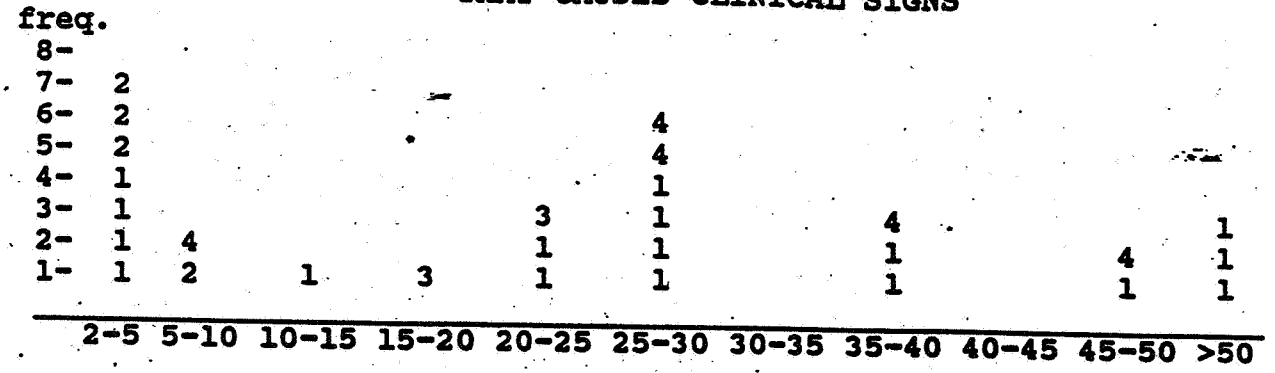
FIGURE 1. FREQUENCY DISTRIBUTION OF DOSAGES OF ALDICARB THAT CAUSED CLINICAL SIGNS



numbers identify the Outbreak.

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D. DISCUSSION

The description of cases used for estimates was limited in terms of symptoms, onset, and severity.

Many of the symptoms of cholinesterase inhibition at low doses, i.e. nausea/vomiting, and diarrhea are non-specific.

The analytical methodology was valid, though the level of detection was somewhat higher at 0.2 ppm than in other reports.

Therefore, there may have been some misclassification errors due to these factors, that is, false positives and false negatives.

Further, the use of sex and age averages for body weights and self reports of food consumption are also subject to some errors of estimation.

Nevertheless, because of the more complete symptomatology reported in the cases with detectable residues, their consistency with the expected syndrome, the validity of the analytical techniques, and the plausibility of the estimates of weight and consumption, these dosage estimates are regarded as valid and reasonable estimates of the potency of Aldicarb.

The weight of the evidence presented here suggest that effects may occur at as little as 2 ug/Kg.

E. REFERENCES

Blondell, Jerome. Alidcarb Watermelon Contamination Report HED Project No. INTRA-0050. Memo of 7/11/90 to W.Sette, SACB/

Goldman, Smith, Neutra, Saunders, Pond, Stratton, Waller, Jackson, and Kizer (1990) Pesticide Food Poisoning from contaminated Watermelons in California, 1985.

Garbus, Joel. 1990 Personal Communication.

At a residue level of 0.2 ppm, a 10 Kg child would have to eat 100 g of commodity to obtain a dose of 0.002 mg/Kg; a 50 Kg woman, 500 g , and a 70 Kg man 700 g.

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

JUL 11 1990

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Aldicarb Watermelon Contamination Report
HED Project No. INTRA-0050

FROM: Jerome Blondell, Health Statistician
Environmental Chemical Review Section
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

THRU: Michael Firestone, Ph.D., Chief
Environmental Chemical Review Section
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

Charles L. Trichilo, Ph.D., Chief
Non-Dietary Exposure Branch
Health Effects Division (H7509C)

TO: William F. Sette, Ph.D.
Science Analysis and Coordination Branch

As requested in Bruce Jaeger's note of June 27,1990, a revised updated report from California titled "Pesticide Food Poisoning from Contaminated Watermelons in California, 1985" by Goldman, Smith, Neutra, Saunders, Pond, Stratton, Waller, Jackson and Kizer has been reviewed in light of the comments that were made on the earlier draft version of this report.

The revised report is superior to the earlier draft. This revision gives a clear epidemiologic account of the investigation of a food contamination incident and its resolution. No attempt is made in the current report to calculate a LOEL based on estimated dosages in the California incident and 3 other outbreaks of aldicarb induced food poisoning, as was done in the earlier draft. Rather the current report, in the discussion section, notes that some illnesses, "clinically compatible with carbamate poisoning" were associated with aldicarb-negative melons, suggesting that health effects can occur at lower than expected levels. This presentation is preferable to the earlier one which made calculations of dose based on what appeared to be unsubstantiated chemical analyses that may not have reflected the true exposure at the time of ingestion.

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The current report gives a clearer presentation of the case definition that was used to distinguish those poisoned by aldicarb-contaminated watermelon. Problems with using symptoms alone to identify cases is demonstrated by Table 4 where most subjects experienced abdominal pain, nausea/vomiting, or diarrhea regardless of whether they were categorized as probable, possible or unlikely cases of aldicarb-induced poisoning. Using a definition involving just these 3 symptoms, the authors calculate a sensitivity rate (true positives) and specificity rate (true negatives) of about 80 percent each. These data indicate there was some difficulty distinquishing poisoned cases from those who were coincidently ill after eating melon. The authors note that poison centers were "overwhelmed with calls" at first so that they did not have time to record complete reports resulting in some cases lost to follow up. It also suggests that a complete listing of symptoms may not have been recorded in each case. Together this information means that the Agency should not put great reliance on any conclusions based on small numbers (1-5) of cases because of the ease with which misclassification may have occurred.

The earlier report made calculations of dose in 17 of the California cases based on analyses from 6 samples of watermelon. Similar calculations were made for 3 other outbreaks of aldicarb poisoning involving 11 cases ingesting watermelon or cucumbers. Little information is provided on the quality assurance procedures that were used to determine the level of aldicarb metabolites. Also it would be desirable to have information demonstrating the stability of aldicarb metabolites from the time of ingestion to the time of analysis. Given these problems and the difficulties with case ascertainment described above, the individual dose calculations should be used with caution.

Assuming accurate chemical analyses, no loss from metabolite breakdown, uniform distribution of the aldicarb metabolite throughout the edible portion of the melon, the 17 California cases received a median dose of 0.027 mg/kg with a range from 0.0032 to 0.060 mg/kg. It would be desirable to have more documentation on the symptoms and timing of symptoms in each of the 17 cases. Even with documentation of aldicarb in the melon, it is possible that a couple of the cases might have experienced coincidental illness. On the other hand, a level somewhat below the median dose could be considered a LOEL given the assumptions stated above. Two other outbreaks cited in the earlier report suggest an even lower LOEL. However, the dosages were calculated on a single samples which are not well documented.

cc: Hank Spencer (TOX Branch)
Bruce Jaeger (SACB)
Aldicarb File
Correspondence File
Circulation

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Aldicarb Food Poisonings in California, 1985–1988: Toxicity Estimates for Humans

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ABSTRACT. Three outbreaks of food poisoning involving watermelons or cucumbers and caused by the carbamate pesticide aldicarb occurred in California between 1985 and 1988. For each outbreak, and for an outbreak of aldicarb poisoning associated with English cucumbers previously reported in the literature, dosages of aldicarb sulfoxide that caused the illnesses were estimated. Estimated dosages ranged between 0.0011 and 0.06 mg/kg body weight, and most were well below the 0.025 mg/kg Lowest Observed Effect Level (LOEL) for subclinical blood cholinesterase depression previously reported for humans. These findings are consistent with aldicarb sulfoxide (ASO) illnesses that have occurred in other states. Aldicarb appears to be more toxic than previously suspected. Scientific and regulatory implications are discussed.

DURING THE PAST 3 y, California has experienced several outbreaks of foodborne poisoning with aldicarb sulfoxide (ASO), a metabolite of the carbamate insecticide aldicarb (Temik®, CAS No. 116-06-3). Aldicarb was developed in 1962 by Union Carbide. The mode of action is rapidly reversible inhibition of acetyl cholinesterase. Signs and symptoms of poisoning include diarrhea, vomiting, lacrimation, salivation, miosis, convulsion, and death. The product is formulated in a granular form for application to soil and uptake by plant roots.

Prior to registration, aldicarb was tested at three dose levels in 12 adult male volunteers.[1] Based on this testing, it was estimated that 0.025 mg/kg was the LOEL for cholinesterase depression. From this study, the National Academy of Sciences extrapolated a No Observed Effect Level (NOEL) for cholinesterase depression of 0.01 mg/kg·d in 1977.[2]

Aldicarb breaks down rapidly (in plants and in the environment) to several metabolites with different toxicities. Figure 1 shows the major metabolic pathways for aldicarb and the acute oral LD_{50} for rats for each compound.[3,4] The two major metabolites of aldicarb are ASO and aldicarb sulfone (AS). ASO has the same LD_{50} as aldicarb; AS has an LD_{50} 27 times higher (i.e., less toxic) and the other, more minor,

*Dr. Beller was formerly with the California Department of Health Services, Preventive Medicine Residency Program.

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metabolites have LD_{50}s 600 to 8 500 times higher (i.e., less toxic).

Because aldicarb is a systemic insecticide (absorbed into roots, stems, leaves and fruit), residues can contaminate the edible portion of food crops. The first known case of aldicarb food poisoning occurred in 1969 when a Washington State employee brought home experimental aldicarb and applied it to roses. Three weeks later his wife ate a single spearmint leaf grown near the roses and developed severe cholinesterase inhibitor symptoms requiring treatment with atropine.[5] In 1977 and 1978, episodes of aldicarb foodborne poisonings occurred in southwestern Nebraska.[6,7] In 1977, nine people ate hydroponically grown (i.e., grown in water) European-type Pandex cucumbers and developed acute illness 15 min to 2 h later. Analysis of the cucumbers revealed a carbamate pesticide that was not specifically identified. In a similar episode in an adjacent city in 1978, ASO was found in cucumbers.

Aldicarb has also been found in groundwater in areas where it was applied. It was first detected in groundwater in Suffolk County, New York, in 1979. Five thousand wells were tested in a 100-square-mile area, and 13.5% were found to have aldicarb levels above 7 ppb, with a mean of 6 ppb and a maximum in one private well of 515 ppb. No associated cases of acute pesticide illness were reported.[8] Since that time, aldicarb-contaminated groundwater has been found in Maine, Florida, California, Arizona, North Carolina, Virginia, and Wisconsin.[9] In Wisconsin, where application to potato crops led to extensive groundwater contamination in Portage County, women who drank water contaminated with aldicarb at concentrations between 1 and 61 ppb and women who drank water uncontaminated by aldicarb were contacted, interviewed, and given immune function tests.[9] Statistically significant positive correlations were found between chronic consumption of contaminated water and elevated skin test response to Candida antigen, increased numbers of T8 lymphocytes, and decreased ratio of T4:T8 cells. Interviews revealed no difference in illness and infection rates, and these findings have yet to be confirmed, but some persisted 2 y later. Likewise, their clinical significance remains unclear.

Widespread use of aldicarb and its ability to persist in groundwater and to be taken up by plants make it important to determine the dose at which acute and chronic illnesses are caused. Aldicarb is not registered for use on watermelons or cucumbers, but it has been implicated in three outbreaks of illness associated with ASO-contaminated watermelons or cucumbers in California and one in Nebraska. These outbreaks were examined to determine what dosages caused illness.

Descriptions of outbreaks

Outbreak 1: Aldicarb sulfoxide in Pandex cucumbers, 1978. In 1978, an investigation in Nebraska of an outbreak of acute diarrhea and vomiting led to the identification of ASO contamination of hydroponically grown European-type Pandex cucmbers. Cholinesterase illness occurred in five persons within 1 h of cucumber ingestion. An extensive epidemiologic and laboratory investigation found ASO in cucumbers from the supermarket and warehouse at 6.6, 9.9, and 10.7 ppm.[6]

Outbreak 2: Aldicarb sulfoxide in watermelons, July 4, 1985. The investigation of the 1985 watermelon outbreak was described in detail in earlier reports.[11] A total of 1 373 illness reports was received, of which 78% were classified as probable or possible pesticide poisoning cases.[11] Illnesses related to watermelon consumption were reported from all regions of California, as well as Oregon, Washington, and Canada. Melons related to some illnesses were traced to Kern County, California. This episode constituted the largest known outbreak of pesticide foodborne illness in North America.[11,12] Because illness occurred in persons who consumed watermelons containing ASO at levels near the lower limit of laboratory detection (i.e., 0.2 ppm in 1985), we were concerned that consumption of melons with undetectable levels of ASO might have caused illnesses, and we therefore estimated the dosages received during this outbreak. Of interest is a 1983 Kern County outbreak of similar gastrointestinal illness associated with watermelon consumption that was reported to the California Department of Health Services (CDHS). In that outbreak, no aldicarb was found, but no assay for ASO was performed.

Outbreak 3: Aldicarb sulfoxide in watermelons, 1987. The CDHS was called in August 1987 by the Kings County, California Department of Health about a family of four seen in the local emergency room after they all became suddenly ill with nausea, abdominal cramping, and vomiting 45 min after consuming slices of a watermelon given to them by a friend. The wife noticed dizziness and sweating, and she vomited and fainted after leaving the emergency room. The melon was analyzed in the laboratory of the California Department of Food and Agriculture (CDFA). Aldicarb was not detected, but ASO was found at 0.3 ppm. The friend admitted to having taken the melon from a nearby field where melons were being grown for seed and aldicarb was applied legally.

Outbreak 4: Aldicarb sulfoxide in English cucumbers, 1988. In May 1988, the CDHS was notified of ASO contamination in hydroponically grown English cucumbers from Redding, California. The Oregon State Health Department had investigated illness reports and identified pesticide contamination. The Oregon investigation led to identification of the distributor and grower of the cucumbers, and prompt embargo and destruction of the product resulted. The Redding grower had shipped a total of 14 cases of cucumbers during the growing season; 13 cases went to Oregon and Washington state, and 1 case went to Sacramento.

There were several illnesses in California associated with this episode (Table 1). One 56-y-old

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Table 1.—Case Reports of Illness Associated with English Cucumbers, California, May 1988

Case	Group	Onset*	Duration†	Classification	Pesticide screening results
1	1	0.75	5.5	Probable	4.67 ppm ASO; 0.54 ppm AS
2	2	1.0	5.0	Probable	1.8 ppm ASO
3	3	1.0	0.5	Probable	No sample available
4	3	1.5	0.5	Probable	No sample available
5	4	1.5	46.0	Probable	Negative Peels only tested
6	5	0.5		Probable	No sample available; store sample neg
7	6	2.0	6.0	Probable	No sample available
8	6	2.0	10.0	Probable	No sample available
9	6	2.5	4.0	Possible	No sample available
10	6	8.0	46.0	Unlikely	No sample available
11	7	0.5	119.0	Probable	No sample available
12	7	8.0	84.0	Unlikely	No sample available
13	8	4.0	18.0	Possible	Negative
14	9	9.5	108.0	Unlikely	Negative
15	10	24.0	4.0	Unlikely	No sample available
16	10	22.0	15.0	Unlikely	No sample available

Notes: ASO = aldicarb sulfoxide, AS = aldicarb sulfone.
*Time in hours between ingestion and onset of symptoms.
†Duration of symptoms in hours.

woman became ill on three separate occasions after eating between 1/6 and 1/3 cucumber. Her symptoms included blurred vision, nausea, diarrhea, abdominal pain, sweating, muscle weakness, dizziness, headache, disorientation, and fatigue. A sample of cucumber tested positive for ASO at 1.8 ppm. A second case, a 66-y-old woman, bought a cucumber on March 29 and ate six slices on April 15. Within 45 min, she experienced nausea, vomiting, sweating, dizziness, loss of balance, disorientation, and fatigue. The cucumber contained 4.67 ppm ASO. Fourteen additional cases were investigated in California.

Methods

For the 1985 watermelon illness episode, a complicated case definition using four categories of cholinesterase symptoms and time of onset of illness was used; it is described in detail in a previous publication.[1] Illnesses were classified as "probable," "possible," or "unlikely" pesticide poisonings based on whether melons were positive for aldicarb metabolites; time of onset of illness, i.e., within 2 h, 2–12 h, or > 12 h; presence of cholinesterase inhibitor symptoms from one or more of four groups, i.e, gastrointestinal, other peripheral autonomic, skeletal muscle, or central nervous system; and whether multiple cases occurred from the same watermelon. For the two California investigations subsequent to the 1985 episode, a simplifed case definition was developed that used nausea, vomiting, and/or diarrhea (n/v/d) within 2 h of produce consumption to identify "probable" cases of carbamate toxicity, other symptoms or onset of n/v/d more than 4 h after consumption for "unlikely" cases, and onset of n/v/d between 2 and 4 h after consumption as "possible" cases. The 4-h cutoff was chosen because, in the 1985 epidemic, it was observed that of all the cases associated with laboratory-positive watermelons, only one had an illness onset time more than 4 h after consumption. Nausea, vomiting, and/or diarrhea were chosen for the symptom definition after analyzing more than 1 000 case reports from the 1985 outbreak and finding that this case definition had 79% sensitivity compared with the more complex definition. It was adopted in response to the need for a simpler case definition for rapid decision-making in field investigations.

Samples of melons and cucumbers from probable cases were requested for laboratory analysis and were collected and shipped by local health departments to the nearest laboratory participating in the investigation. Informants reporting illnesses were instructed to wrap the remainder of the suspect watermelon or cucumber in aluminum foil and freeze it until someone could come to take it to the laboratory. Specimens were collected by personnel from either CDFA or CDHS.

Analyses for aldicarb, ASO, and AS in watermelons and cucumbers were performed by the CDFA. In addition, for outbreak 1, several confirmatory analyses were performed by the U.S. Food and Drug Administration (FDA) regional laboratory and CDHS Food and Drug Laboratory. Analyses were performed by CDFA and FDA using liquid chromatography with post-column derivatization using orthophthalaldehyde and fluorometric detection of derivatives. Minimum detection levels ranged between 0.1 and 0.5 ppm ASO, depending on the year and the

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laboratory. Confirmatory analyses by CDHS were performed using gas chromatography and a method developed by Union Carbide for detecting aldicarb residues in water [method ALDICARB-FPD-WATER(a)].[13] The detection level by this method for all aldicarb residues combined was 0.01 ppm. Laboratory-positive produce contained ASO and, occasionally, AS (Fig. 1). Because AS, when present, was found in small concentrations and because AS is much less toxic than ASO, dosages were calculated for ASO only.

Dosage calculations. In no case was the parent compound aldicarb found. Dosages were calculated using age and sex to derive expected body weight and using self-reports of amount consumed to derive consumption estimates. The edible portion of an average watermelon weighs 16 lb (7 300 g). It is assumed that a semicircular slice of watermelon contains 454 g (1 lb) of edible fruit. (This was validated by weighing slices before and after consumption by several CDHS staff members.) It is assumed that an average cucumber weighs 235 g (the mean of 300 g for large and 170 g for small cucumbers) and that cucumbers were not peeled before being consumed. Because their toxicities are similar,[1] dosages of ASO were compared with the NOEL and LOEL for aldicarb.

Results

Dosage calculations. For outbreak 1, we estimated the dosage received for the five cases reported (Table 2).[14] A range of estimates is given because the cucumbers that caused illness had been consumed

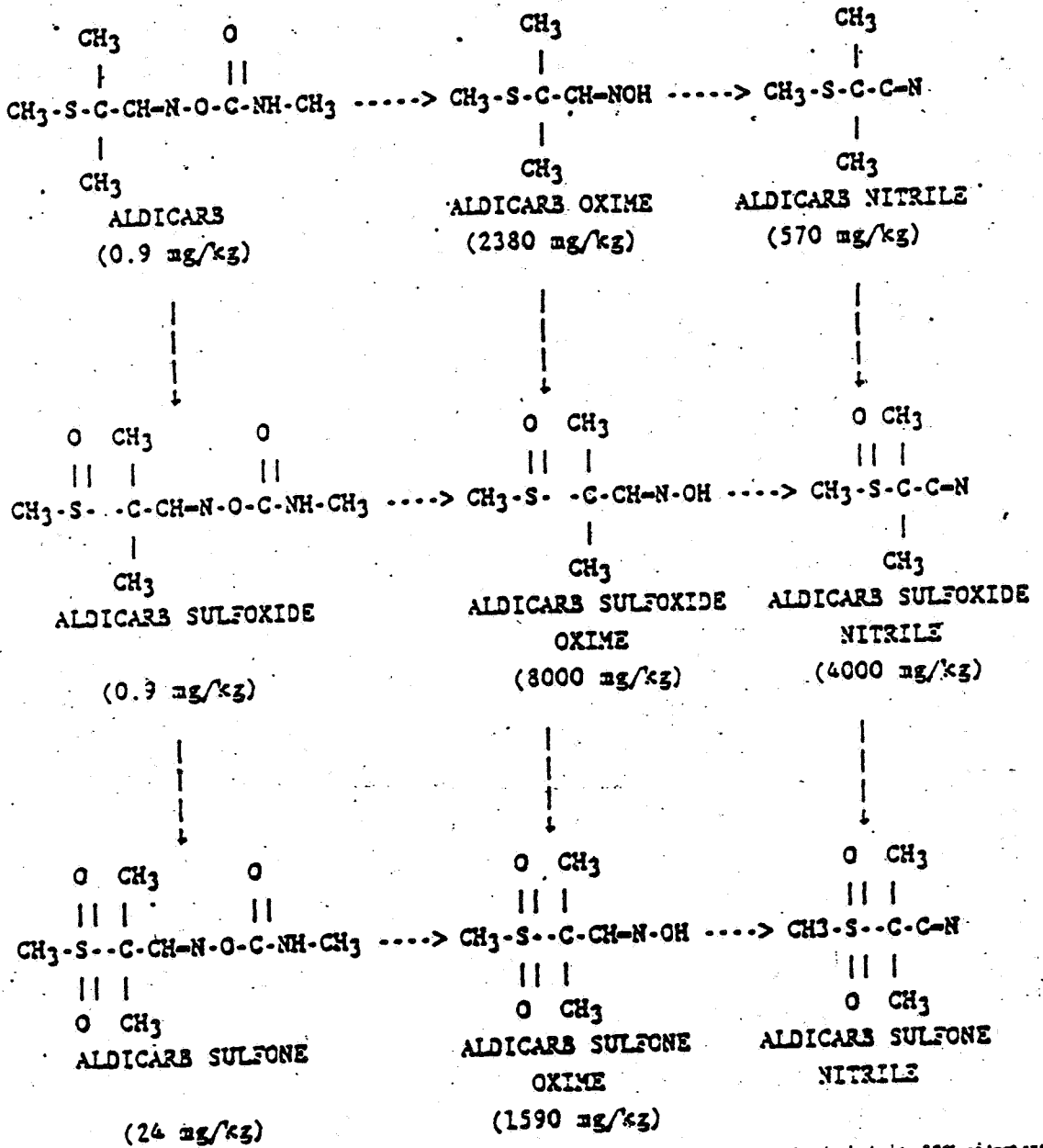

Fig. 1. The metabolism of aldicarb.2. Numbers within parentheses are = LD_{50}, i.e., dose estimated to be lethal to 50% of test rats.

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Table 2.—Dosage Calculations for Persons with ASO-Positive Melons, California 1985, 1987, and 1988, and Nebraska 1978

Case	Group	ASO (ppm)	Age	Sex	Amount eaten*	Wt. (kg)†	Dosage (mg/kg)	Comments
Outbreak 1, Nebraska, cucumber (1978):								
1	1	6.6–10.7	23	M	1 cucumber	70	.022–.036	
2	1	6.6–10.7	6	M	½ cucumber	22	.035–.057	
3	2	6.6–10.7	40	F	?(1 cucumber)	57	.027–.044	
4	3	6.6–10.7	49	F	¼ cucumber	57	.020–.033	
5	3	6.6–10.7	49	M	¼ cucumber	70	.006–.009	
Outbreak 2, watermelon (1985):								
1	1	3.3	16	F	1 slice	56	0.027	‡
2	1	3.3	11	M	1 slice	37	0.040	‡
3	1	3.3	Adult	F	1 slice	57	0.026	
4	2	3.0	29	F	<⅛ melon	57	0.060	
5	2	3.0	32	F	1 slice	57	0.024	
6	2	3.0	58	F	½ slice	57	0.012	
7	2	3.0	40	F	⅛ melon	57	0.030	
8	3	2.7	62	F	⅛ melon	57	0.054	§
9	4	1.2	65	F	4 slices	57	0.038	
10	4	1.2	46	F	3 slices	57	0.029	
11	4	1.2	24	F	3 slices	57	0.029	
12	4	1.2	13	F	5 slices	46	0.059	
13	5	0.76	38	F	⅛ melon	57	0.015	
14	6	0.4	51	F	½ slice	57	0.0021	
15	6	0.4	50	M	1 slice	70	0.0026	
16	6	0.4	14	M	1 slice	54	0.0034	
17	6	0.4	22	F	1 slice	57	0.0032	
Outbreak 3, watermelon (1987):								
1	1	0.3	37	M	2 slices	70	0.0020	
2	1	0.3	35	F	2 slices	57	0.0048	
3	1	0.3	12	F	1 slice	41	0.0017	
4	1	0.3	8	F	1 slice	26	0.0011	
Outbreak 4, cucumber (1988):								
1	1	4.67	66	F	6 slices	57	0.0023	
2	2	1.8	56	F	⅛–½ cuc.	57	0.0074	

*Amount eaten was used to estimate grams consumed.
†Weight was estimated using the average for age and sex.
‡Admitted to the hospital.
§Bradycardia treated with atropine in an emergency room.

entirely, and dose calculations were based on test results of cucumbers collected from the store and warehouse. Calculated dosages of ASO ranged between 0.0011 and 0.057 mg/kg body weight.

For outbreak 2, ASO concentrations were available for six watermelons. Using self-reports of amount of melon eaten (number of slices or fraction of a watermelon), and assuming normal weight for age and sex, and approximate ASO dosage for 17 of the 19 individuals consuming these six melons was calculated (Table 2). (Two cases had incomplete information on amount consumed.) Estimated dosage ranged from 0.0026 to 0.060 mg/kg, with a median of 0.027 mg/kg body weight. It should be noted that all but case number 4 were initially classified as "probable" cases; case number 4 was classified as a "possible" case because the onset time was 6.5 h. For the six melons examined, there was no correlation between holding time prior to analysis and level of ASO found. In fact, one of the highest concentrations, 2.7 ppm, was in a melon that was reportedly unrefrigerated for 2 wk.

For outbreak 3, the watermelon associated with illness contained 0.3 ppm ASO, and the dosages calculated ranged between 0.0011 and 0.0048 mg/kg body weight (Table 2).

For outbreak 4, there were 16 illness reports in 10 clusters investigated in California. Samples of the cucumbers eaten were obtained from homes for 11 cases; for a 12th case, a sample was taken from the store where the cucumber was purchased. The cases are described in Table 1. For two probable cases, cucumbers were positive for ASO, and one also contained AS. Dosages were 0.0023 and 0.0074 mg/kg body weight (Table 2).

Figure 2 shows the range of ASO dosages estimated for the four outbreaks and the current NOEL and LOEL for aldicarb. For all four outbreaks, illness

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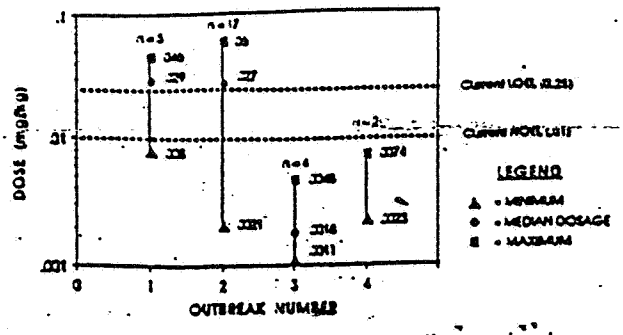

Fig. 2. ASO dosage estimates for foodborne illness outbreaks.

was observed at estimated dosages below the current aldicarb NOEL. Median estimated ASO dosages were at or well below the current aldicarb LOEL.

Theoretical calculations. The estimated ASO dosages causing illness in these outbreaks can be used to calculate whether a 70-kg person could ingest a sufficient quantity of produce contaminated with ASO at just below the detection limit of 0.2 ppm to develop illness. At the lowest dosage associated with illness, i.e., 0.0011 mg/kg body weight, the amount of watermelon (or cucumber) required to effect illness would be 380 g (about a slice of watermelon or cucumber). If a 10-kg child consumes 500 g (or just over one slice) of watermelon contaminated with ASO at the detection limit of 0.2 ppm, the dosage would be 0.01 mg/kg body weight, which is well above the lowest toxic dose we calculated.

Discussion

Epidemiologic studies of aldicarb-related food poisoning outbreaks suggest that illness can be caused at much lower levels than those previously described when the compound was first registered for use. Furthermore, it appears possible that illness may be caused by produce with contamination below the detection level of screening assays that are used by regulatory agencies. Although use of such epidemiologic data is an unconventional way of measuring pesticide toxicity, findings were very consistent between outbreaks and over time, and in different laboratories. In addition, there is some evidence for a dose-response. For California investigations (outbreaks 2, 3, and 4), more severe illnesses requiring hospital treatment occurred only for cases with estimated dosages greater than 0.01 mg/kg body weight. The only case reported who required atropine treatment had the second highest estimated dosage, i.e., 0.054 mg/kg body weight (Table 2). Evidence for a dose-response lends credence to the conclusion that these estimated dosages approximate the actual dosages and were responsible for illnesses.

The estimated dosages for these outbreaks range between 0.0011 and 0.06 mg/kg body weight. In contrast to ASO levels found in these illness outbreaks, aldicarb levels in groundwater (between 1 and 100 ppb) are associated with lower daily dosages. For example, a 70-kg person who consumes 2 l of water contaminated with 10 ppb ASO would receive 0.00028 mg/kg body weight. However, a 10-kg child who drinks 1 l of water per day that contains 10 ppb ASO would have a daily dosage of 0.001 mg/kg-d. If, as our analysis suggests, illness can be caused by a 0.0011 mg/kg body weight dose of ASO, then there is no margin of safety between the dose the child receives and toxic effects.

Based on a small group of human subjects, dosages associated with foodborne illness episodes were sometimes much lower than the 0.025 mg/kg LOEL and 0.01 mg/kg/d NOEL (Fig. 2). However, there are two primate studies that show cholinesterase depression at 0.005 mg/kg body weight.[15,16]

It is important to consider possible sources of bias in this study. Our dosage calculations are somewhat uncertain because they are based on self-reports of consumption, estimates of weight consumed, and estimated body weight. However, it is difficult to imagine how this could have resulted in estimates one to two orders of magnitude between the LOEL and our results. Furthermore, dosage estimates from the four outbreaks are remarkably congruent. Possibly, if ASO degraded between the time of consumption of contaminated produce and the time the produce was tested, the actual dosages were greater than our estimates. However, for outbreak 2, no relationship was found between ASO level and delayed laboratory testing. It is also possible that the earlier report[1] was based on a small group of healthy subjects employed by the manufacturer, and the study missed toxicity that may occur in lower dosages in more sensitive individuals.

Possible alternative explanations for these findings must be mentioned. It is unlikely that the illnesses in these individuals resulted from an increased genetic susceptibility to ASO among cases, because many of the multiperson illness episodes in outbreak 2 were among unrelated individuals. For example, six truck drivers who snacked on a watermelon containing ASO all became ill, although they were not related to each other. It is also possible that ASO is much more toxic to humans than the parent compound. Another possible explanation is that local gastrointestinal cholinesterase effects can occur and cause illness at dosage levels below those causing significant blood cholinesterase depression. Blood cholinesterase is not neuronal cholinesterase, and it is possible that gastrointestinal neuronal cholinesterase levels are more suppressed than blood levels when aldicarb is ingested orally. None of the subjects studied had blood drawn for cholinesterase levels within 4 h after eating contaminated produce, and because aldicarb has a short duration of action, it was not possible to compare symptoms with blood cholinesteriase activity. Finally, it is difficult to eliminate the possibility that other toxic metabolites of aldicarb were present but were not detectable or measured in the laboratory.

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Of interest is that all of these outbreaks have involved the fruits of members of the cucurbitaceae family, which includes cucumbers, melons, squash, and pumpkins. Aldicarb, when dissolved in water, is taken up by the roots and deposited in the fruit of plants in this family. It is unknown why misuse has occurred in hydroponically grown cucumbers in particular, but it seems reasonable to hypothesize that the pesticide may have been on the premises for treating ornamentals, and there may have been employee error and/or greenhouse pest problems leading to its misuse. Although the California experience implies that the problem can result either from mixture with water in hydroponics or from application to soil in granular form, usage in hydroponics may be of particular concern because of persistence of aldicarb in water.

Many questions about aldicarb and its metabolites remain unanswered:

(1) What is the additive toxicity of aldicarb and its metabolites in heterogeneous human populations?

(2) Are there unknown aldicarb metabolites in produce that are not detectable at levels that can cause severe toxicity?

(3) What is the half-life of aldicarb in cucumbers, melons, and other crops?

(4) Do cholinesterase inhibitor pesticides act directly on the gastrointestinal tract at dosages lower than those associated with blood cholinesterase inhibition?

These questions have regulatory and epidemiologic significance. Recently, the U.S. Environmental Protection Agency conducted a review of aldicarb toxicity and the impact on groundwater. In 1988, they estimated that between 5.2 and 5.7 million pounds of aldicarb were applied annually in the United States.[17] Until these questions are answered, it will be necessary for state and local health departments to continue to vigorously monitor illness reports for aldicarb toxicity.

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References

1. Haines RG. Ingestion of aldicarb by human volunteers: a controlled study of the effect of aldicarb on man. Unpublished report. Union Carbide Corporation; 1971. Reported in National Academy of Sciences. National Resources Council. Drinking water and health 1977; 635–43.
2. National Academy of Sciences, National Resources Council. Drinking water and health. 1977.
3. Risher JF, Mink F, Stara JF. The toxicologic effects of the carbamate insecticide aldicarb in mammals: a review. Environ Health Perspect 1987;72:267–81.
4. United Nations Food and Agriculture Organization. Pesticide residues in food—1979 evaluations. Rome, 1980.
5. Marshall E. The rise and decline of Temik (TM). Science 1989;229:1369–71.
6. Goes AE, Savage EP. Gibbons G, et al. Suspected foodborne carbamate pesticide intoxications associated with ingestion of hydroponic cucumbers. Am J Epidemiol 1980;111:254–60.
7. Centers for Disease Control. Suspected carbamate intoxications. Nebraska. MMWR 1979;28:133–34.
8. Zaki MH, Moran D, Harris, D. Pesticides in groundwater: the aldicarb story in Suffolk County, NY. Am J Pub Health 1982; 72:1391–95.
9. Fiore MC, Anderson HA, Hong R, et al. Chronic exposure to aldicarb-contaminated groundwater and human immune function. Environ Res 1986;41:633–45.
10. Mirkin IR, Anderson HA, Honrahan L, et al. Changes in T-lymphocyte distribution associated with aldicarb-contaminated drinking water: a follow-up study. Environ Res 1990; 51: 35–50.
11. Centers for Disease Control. Aldicarb food poisoning from contaminated melons—California. MMWR 1986; 35:254–58.
12. Green MA, Heumann MA, Wehr HM, et al. An outbreak of watermelon-borne pesticide toxicity. Am J Pub Health 1987; 77:1431–34.
13. Union Carbide Corporation. ALDICARB-FDP-WATER(a). Agricultural Products Co., Inc., Research and Development Department, P. O. Box 3361, South Charleston, West Virginia 25303. March 1980.
14. Goldman, LR, Jackson RJ. Letter to the editor. JAMA 1986; 256:23, 218.
15. Union Carbide. Aldicarb foodborne residue toxicity study in monkeys-bananas. Unpublished report. Union Carbide Corporation, 1987. Reported in U.S. Environmental Protection Agency. Office of Pesticides and Toxic Substances. Aldicarb special review technical support document. Washington, D.C., June 1988.
16. Union Carbide. Aldicarb foodborne residue toxicity study in monkeys-watermelons. Unpublished report. Union Carbide Corporation, 1987. Reported in U.S. Environmental Protection Agency. Office of Pesticides and Toxic Substances. Aldicarb special review technical support document. Washington D.C., June 1988.
17. U.S. Environmental Protection Agency. Office of Pesticides and Toxic Substances. Aldicarb special review technical support document. Washington, D.C., June 1988.

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Pesticide Food Poisoning from Contaminated Watermelons in California, 1985

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ABSTRACT. Aldicarb, a carbamate pesticide, is the most potent pesticide in the market and has a LD_{50} of 1 mg/kg. In the United States it is illegal to use aldicarb on certain crops, e.g., watermelons, because it is incorporated into the flesh of the fruit. Once an accidental or illegal use of such a potent pesticide occurs, there is no easy way for the agricultural or public health system to protect the populace. This paper describes the impact of one such event upon the health of individuals and the institutions of California. On July 4, 1985, California and other western states experienced the largest known outbreak of food-borne pesticide illness ever to occur in North America. This was attributed to watermelons contaminated through the illegal or accidental use of aldicarb by a few farmers in one part of the state. Within California, a total of 1 376 illnesses resulting from consumption of watermelons was reported to the California Department of Health Services (CDHS). Of the 1 376 illnesses, 77% were classified as being probable or possible carbamate illnesses. Many of the case reports involved multiple illnesses associated with the same melon among unrelated individuals. Seventeen individuals required hospitalization. There were 47 reports of illness

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involving pregnant women, two of whom reported having subsequent stillbirths. Thirty-five of the remaining pregnant women were followed–up 9 mo after the epidemic; no additional stillbirths were found. To control the epidemic, it was necessary to embargo on July 4 and to destroy all watermelons in the state on July 7 and to effect a field certification program. The epidemic and the costly resultant control measures illustrate the difficulties in assuring the safe use of the most potent pesticide. The use of pesticides is controlled by an elaborate set of crop specific regulations. State and federal regulators use laboratory tests of produce samples to insure that regulations are followed. When inadvertent or illegal applications of pesticide occur in a particular crop, there is no system that guarantees that the public will not be exposed. For most pesticides, the effects may not be dramatic, but when a potent pesticide appears in a widely eaten commodity, the impact on health and the institutions that are designed to protect it can be devastating. This paper describes the course of one such event.

ON JULY 3, 1985, the Oregon Department of Health notified the California Department of Health Services (CDHS) of several cases of possible pesticide illness related to consumption of watermelons that were thought to have been grown in Arizona.[1,2] At 4:00 A.M. on July 4, a 62-y-old woman on digoxin therapy was treated at a Lake County, California, emergency department for hypotension, severe bradycardia (31 beats per minute [bpm]), atrial fibrillation, diaphoresis, vomiting, diarrhea, lacrimation, salivation, and muscle twitching. She had eaten watermelon about 30 min earlier. Her symptoms resolved following treatment with atropine. Two other family members who had consumed the same watermelon were also ill and had similar though milder symptoms. The treating physician notified the San Francisco Bay Area Regional Poison Control Center, which subsequently notified CDHS.

Later on the morning of July 4, Oregon officials reported to CDHS that aldicarb sulfoxide (ASO), a toxic degradation product of aldicarb, had been detected in several of the melons related to illness episodes in that state and that the origin of the melons was, in fact, from California.[1,2] Aldicarb, CAS No. 116-06-3, is a cholinesterase-inhibiting carbamate pesticide that is not registered for use on watermelons in the U.S. but commonly used on citrus, cotton, potatoes, peanuts, and soybeans. Within 2 h, calls to 10 California poison control centers, 20 selected emergency departments, and 1 county health department had identified an additional 12 presumed cases of pesticide illness related to consumption of watermelons. This included a group of 4 individuals in Bakersfield who had eaten a striped melon purchased at a roadside stand, a group of 6 individuals who had eaten a striped melon from a Los Angeles-area supermarket warehouse, and 2 individuals in the San Francisco Bay Area who had eaten green melons purchased at different retail stores. These illnesses were investigated by state and local health officials, and arrangements were made for obtaining watermelon samples.

Just prior to noon on July 4, statewide media advisories were issued that warned against eating watermelons, and an embargo was placed on the sale of watermelons throughout California. Usual product recall mechanisms were inoperative because the day was a national holiday. By late afternoon on July 4, case investigations and tracking of sources of melons back through the distribution chains had implicated a single Kern County shipper in several, but not all of the episodes. Subsequently, in the melon from the first known California case, ASO was found at 2.7 parts per million (ppm). The embargo remained in effect for the next 3 d.

On July 7, all watermelons in retail outlets or in the chains of distribution were destroyed because it was impossible to distinguish ASO-contaminated melons from melons free of ASO. A field certification program was implemented on July 10, and the embargo was lifted. Surveillance after that time identified only one further illness episode in California associated with a melon that tested positive for ASO. Product certification was conducted by the California Department of Food and Agriculture (CDFA) and involved testing composite samples of melons from fields for aldicarb and its metabolites. Melons from fields that tested negative were labeled by CDFA to certify that they had been cleared.

Methods

Commencing late on the morning of July 4, the public was advised through the mass media to report any watermelon-associated illness to their local health department. An active surveillance network set up by CDHS on July 5 involved (a) daily calls to California's 10 regional poison control centers and selected emergency departments, (b) daily contact with all local health departments in California, and (c) periodic calls to several western states and the western provinces of Canada. Local health departments were asked to complete and return an illness report form (described below) to CDHS for all cases reported to them. They were also asked to periodically call selected hospital emergency departments within their jurisdiction so as not to miss illnesses severe enough to require emergency treatment or hospitalization.

The CDHS illness report form and a case-definition algorithm were developed based on the expected cholinergic symptoms resulting from ingestion of aldicarb (Table 1). The case definition divided illness reports into three categories: (1) probable, (2) possible, or (3) unlikely, depending on timing of symptom onset, nature and severity of

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symptoms, and number of people ill from the same melon.

The CDHS illness report forms were distributed rapidly to local health department officials in an effort to speed collection of uniform case information. The forms included questions about symptoms, time and location of melon purchase, and others who ate the same melon. All reports of illness with date of onset after July 10 were telephoned to CDHS and promptly reviewed by a physician to identify probable poisoning cases from melons bearing certification labels. Additional information was sought from persons who reported illness, if necessary. Samples of melons from probable cases were collected and shipped by local health departments to the nearest participating CDFA or CDHS laboratory for analysis.

Analyses for aldicarb, ASO and aldicarb sulfone (AS) in watermelons were performed by CDFA. In addition, several confirmatory analyses were performed by the U.S. Food and Drug Administration (FDA) regional laboratory in Los Angeles and CDHS's Food and Drug Laboratory. Analyses by CDFA and FDA were performed using liquid chromatography. The minimum detection level was usually 0.2 ppm but ranged between 0.1 and 0.5 ppm ASO. Confirmatory analyses by CDHS were performed using gas chromatography and a method developed by Union Carbide for detecting aldicarb residues in water [method ALDICARB-FPD-WATER(a)].[3] The detection level by this method for all aldicarb residues combined was 0.01 ppm.

Selection of melons for testing was completed in two stages. During the first stage, i.e., prior to July 10, attempts were made to confirm the source and extent of the epidemic. The second stage, after July 10, involved sampling melons from fields that had passed the certification program. The theoretical ability of the field certification sampling plan to detect a single, highly contaminated field was quite good, but given the practical limit of detection of ASO, the necessary compositing of samples, and the large number of fields involved, it was still possible that some contaminated melons might have reached retail markets. Therefore, melons associated with "probable" illnesses that occurred after July 10 were assigned top priority for testing.

Active surveillance continued until the end of August 1985. All case reports were reviewed later for completeness, and additional data were sought when needed. Data from individual case reports were then analyzed using the standardized case definition.

In March 1986, an attempt was made to contact by mail and telephone the 47 women who reported being pregnant when they experienced their watermelon-associated illness. Information was obtained on the pregnancy outcome, birthing complications, birth defects, and any other relevant problems. Six of the 47 were lost to follow-up. Of the remaining 41, 2 denied having been pregnant, and 1 refused to participate. The other 38 women provided information on a standard questionnaire about the outcome of the pregnancy and the baby's health.

Case reports were tabulated in an attempt to identify the geographic source(s) of the epidemic. Illness rates and numbers of illness were mapped by county using SAS/GRAPH, 1980 U.S. Census population denominators, and Tektronix plotter.[4] In an attempt to pinpoint store chains (and through them, wholesalers and farmers) who might have sold contaminated melons, we compared the frequency with which the various chains were identified by "probable" cases and by "unlikely" cases. Our reasoning was that "unlikely" cases probably approximated a random sample of the population as to their use of the various store chains so that we could analyze the data as one would a case-control study. We calculated odds ratios and 95% confidence limits. This measure of association divides the odds of using a particular store chain by "probable" cases by the odds of using that chain among "unlikely" cases. For rare diseases, it is an estimate of the rate ratio, i.e., the incidence of poisoning in patrons of that chain divided by the incidence in nonpatrons. Distributors that served counties or store chains with high odds ratios would be most suspect as sources for contaminated watermelons.

Because of the difficulty in using the complete case definition given in Table 1, which required asking cases about the occurrence of multiple symptoms in several categories, simpler alternative case definitions were explored using data on symptom rates and onset times.

Results

Active surveillance. Case reports were received for dates as early as June 1, 1985. Table 2 shows the number of case reports received in California for the period of active surveillance (June–August 1985) by case classification. In all, 1 376 case reports were received; 78% were classified as probable or possible pesticide poisoning. The geographic distribution of illnesses was evaluated in an attempt to identify the origin of the contaminated melons, but mapping did not suggest a source or sources. Analysis of stores where melons associated with pre-July 10 illness were purchased showed that there were four major supermarket chains involved. Only one of these had a significantly elevated odds ratio, 1.89 (95% confidence limits 1.00 and 3.56), for "probable" vs. "unlikely" illness reports. However, the watermelon distribution systems were too intermingled to quickly determine the suppliers for this chain.

The majority of incidents (61%) involved one person becoming ill after eating a melon. Twenty-two percent of the reports involved 2-person episodes; 10% were 3-person clusters, and 3% were 4-person clusters. Additional clusters involving 5, 6, 9, and 13 persons becoming ill after eating from the same melon also were reported.

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Table 1.—Case Definitions for Watermelon-Associated Illness Outbreak—California, July 1985

Classification of Cholinergic Symptoms

Group 1: Gastrointestinal
- Abdominal pain
- Nausea and/or vomiting
- Diarrhea

Group 2: Other peripheral autonomic
- Blurred vision and/or watery eyes
- Pinpoint pupils
- Excess salivation
- Sweating or clamminess

Group 3: Skeletal muscle
- Muscular weakness
- Twitching

Group 4: Central nervous system
- Seizures
- Disorientation or confusion
- Excitation

Classification of Illness Reports

1. **Probable case:**
   Melon positive for aldicarb or aldicarb metabolites; onset ≤ 2 h after consuming melon; AND ONE OF THE FOLLOWING: Multiple groups of cholinergic symptoms or a single group of symptoms and more than one person ill from the same melon; OR onset between 2 and 12 h after consuming melon, multiple symptom groups, and more than one person ill from the same melon.
2. **Possible case:**
   Onset less than 2 h after consuming melon, a single group of symptoms, and no other illnesses reported from the melon; OR onset within 2 to 12 h after consuming melon and multiple symptoms or symptoms from only one group.
3. **Unlikely case:**
   Some other cause of illness judged to be more likely; OR any illness with onset of symptoms more than 12 h after eating melon.

Table 2.—Numbers and Percentages of Watermelon-Associated Illnesses Reported in California, June 1–August 31, 1985, by Onset Date and Case Definition

Case definition	Onset 6/01–7/10		Onset 7/11–8/31		Onset unknown		Total	
Probable	493	(49%)	197	(57%)	2	(8%)	692	(51%)
Possible	269	(27%)	101	(29%)	6	(23%)	376	(27%)
Unlikely	195	(19%)	40	(12%)	0	. . .	235	(17%)
Incomplete	48	(5%)	7	(2%)	18	(69%)	73	(5%)
Total	1 005	. . .	345	. . .	26	. . .	1 376	

Note: See Table 1 for case definition.

Figure 1 shows the epidemic curve of probable watermelon illness reports within California by date of purchase of melons. The first probable case was reported for a melon purchased June 16; reports rose sharply thereafter. Reports peaked for melons purchased on July 3. There was an abrupt decline in reports for melons purchased after July 4, which coincided with the melon embargo, media advisories, and other measures. Illness onsets for probable cases peaked July 4, and, as with onsets by purchase date, sharply declined after July 4.

Severity of illness. Most people had relatively short-term minor illnesses that resolved quickly; however, some were severely ill. Several reports of cardiac arrhythmias, dehydration, seizures, and other severe illnesses were associated with watermelon consumption before and after July 10 (Table 3). Overall, 17 persons were reported to require hospital admission, 16 of whom were admitted prior to July 10. Of 6 reported deaths, all of which were autopsied, none could be attributed by the coroners to aldicarb/ASO ingestion.

Pregnancy outcomes. Of the 38 women pregnant when they had watermelon-associated illness, 18 were classified as probable cases, 9 as possible, and 10 as unlikely. In one case, the information to classify the illness was inadequate. During the two months immediately after the incident, three pregnancies were investigated. Two near-term pregnancies resulted in stillbirths following acute illnesses associated with watermelon consumption. One pregnant woman had a "probable" illness, and the other had a "possible" illness. Fetal tissues from both stillbirths tested negative for aldicarb and its metabolites (personal communication, Union Carbide Corporation, 1985).

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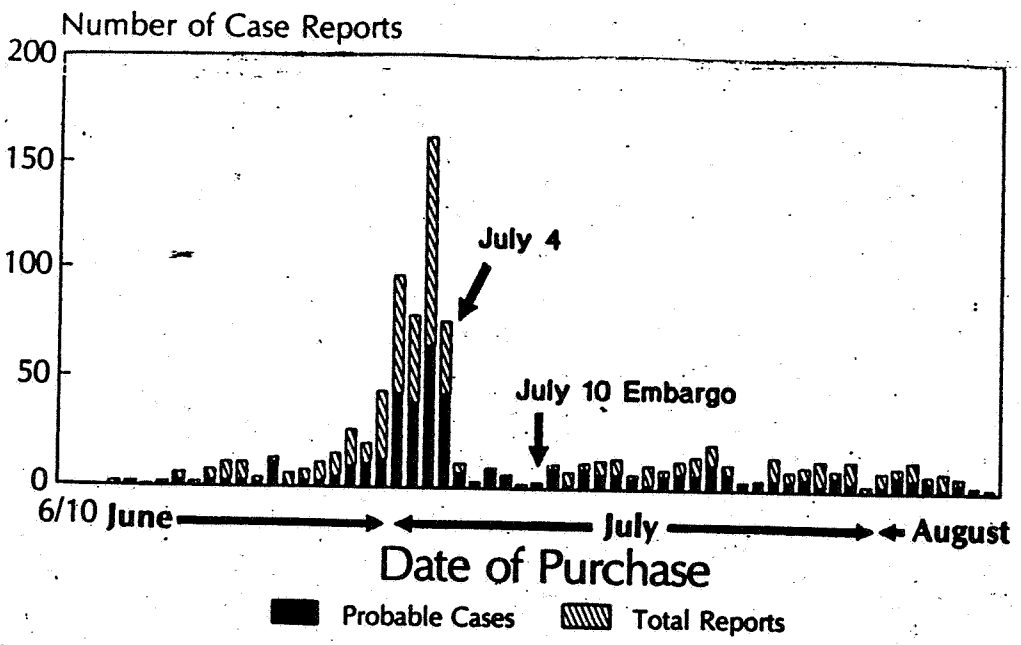
Fig. 1. Watermelon aldicarb illness reports by case definition and melon purchase date California, 1986.



Nine months later an attempt was made to contact the other women who reported being pregnant when they had their watermelon-associated illness. Among the 35 women contacted, 2 neonatal deaths were reported. One was a premature infant born to a mother with "possible" illness, who reported headache and fever 1 wk prior to delivery, raising the possibility that the premature birth and death may have been due to an infection. The second death was due to hypoplastic left heart syndrome; this occurred to a mother with a "probable" illness during the 25th wk of gestation.

Laboratory testing. Of 62 laboratory-tested melons purchased prior to July 10 and associated with illness, 9 (14.5%) were ASO positive. For illnesses associated with melons purchased after July 10, 188 melons were tested, and 1 (0.5%) was ASO positive. In no case was the parent compound aldicarb identified, but some melons contained AS. In addition to the 1 noted aldicarb-positive melon purchased in California after July 10, 2 other aldicarb-positive CDFA-labeled watermelons associated with illness after July 10 were reported in Canada (personal communication, 1985) and Oregon.[1] One of the 3 positive melons found after July 10 could be traced to a particular California field.

Case definition.

The case definition algorithm was compared with symptom reports (Table 4). In general, the 28 with laboratory confirmation of watermelon contamination with ASO were more likely to have had symptoms compatible with carbamate poisoning than those for whom melon tests were negative or not performed. Symptoms reported by at least 50% of those who consumed confirmed ASO-contaminated melons included abdominal pain, nausea, vomiting, diarrhea, blurred vision, salivation, sweating, muscle twitching and/or weakness, and disorientation. These symptoms were also found, but with less frequency, among cases classified as probable, possible, and unlikely. Symptom group 1 (gastrointestinal symptoms) showed the smallest differences in reporting between laboratory-confirmed melon

Table 3.—Severe Illness in California Associated With Watermelon Consumption, Summer 1985.

Condition	Number of cases reported	
	Before July 10	July 10 and after
Seizures	3	0
Loss of consciousness	4	1
Cardiac arrhythmia	6	1
Hypotension	4	0
Dehydration	17	2
Anaphylaxis	3	0

Note: Some individuals had more than one of the above symptoms.

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Table 4.—Cases With Various Symptoms, by Case Definition*: California Aldicarb in Watermelon Episode, 1985 †

Symptom	Melon positive‡ for ASO	Illness report classification		
		Probable	Possible	Unlikely
(Total)	28 (100.0)§	689 (100.0)	311 (100.0)	303 (100.0)
Group 1				
Abdominal pain	23 (82.1)	493 (71.6)	212 (68.2)	158 (52.2)
Nausea/vomiting	24 (85.7)	563 (81.7)	250 (80.4)	200 (66.1)
Diarrhea	24 (85.7)	466 (67.6)	179 (57.6)	181 (59.7)
Group 2				
Blurred vision	17 (60.7)	223 (32.4)	31 (10.0)	40 (13.2)
Salivation#	14 (50.0)	128 (18.6)	22 (17.1)	21 (6.9)
Sweating#	20 (71.4)	356 (51.7)	61 (19.6)	59 (19.5)
Group 3				
Muscle//	15 (53.6)	222 (32.2)	41 (13.2)	40 (13.2)
Group 4				
Disorientation	17 (60.7)	208 (30.2)	36 (11.6)	45 (14.9)
Other symptoms				
Breathing**	2 (7.1)	20 (2.9)	4 (1.3)	5 (1.6)
Urination††	5 (17.9)	150 (21.8)	21 (6.8)	22 (7.3)
Fever‡‡	4 (14.3)	151 (21.9)	44 (14.2)	52 (17.2)
Hearing problem	0 (0)	20 (2.9)	9 (2.9)	5 (1.7)

*See Table 1.
†Excludes 45 cases that could not be classified and with untested melons.
‡Not mutually exclusive from other classifications. ASO is a metabolite of aldicarb.
§Values are given as number and percentage, which appear in parentheses.
#Excessive salivation or sweating.
//Muscle weakness and/or twitching.
**Difficulty breathing or shortness of breath.
††Excessive urination or incontinence. Was not included in case definition because of likelihood of urination associated with consumption of a large amount of watermelon.
‡‡As noted by respondent.

cases and the other case groups, and therefore may be the least specific of the cholinesterase inhibitor symptoms. Fever was reported by 14.3% of those who consumed laboratory-positive melons and by 14% to 22% of those in the other groups. Fever was included to differentiate those persons with infectious illness (e.g., viral gastroenteritis), but it failed to do this (possibly because fever was self-reported). To screen for over-reporting, questions were asked about hearing problems; less than 3% of persons in any category reported same.

Several simpler case definitions were developed for illness that occurred within 2 h of watermelon consumption. The following symptom patterns were compared to the more complex case definition used for this outbreak: diarrhea only, nausea and/or vomiting only, diarrhea and nausea/vomiting, and diarrhea or nausea/vomiting. For the four definitions, sensitivity and specificity were calculated. Diarrhea *or* nausea/vomiting within 2 hr of watermelon consumption had the highest sensitivity (79%) and specificity (82%). Hence, if cases with ASO-positive melons had been classified on the basis of these two symptoms alone, 79% of the cases defined as "probable" using the complete definition would have been identified.

Cantaloupe-associated illness. In addition to the reports of watermelon-related illness, there were in this same period 77 illness reports associated with consumption of about 25 cantaloupes. Many of these cantaloupes were tested, and all tested negative for ASO. About half were tested for other pesticide residues (i.e., carbamates, organophosphates, and chlorinated pesticides); none were found. A few complaints about other types of fruit (e.g., honeydew melons) also were received, but none could be linked to any pesticides.

Discussion

Aldicarb is the most acutely toxic pesticide registered in the United States. It has two primary breakdown products: (1) ASO (for rats, LD_{50} = 0.9 mg/kg) and (2) AS (for rats, LD_{50} = 24 mg/kg).[5] With well over 1 000 reports of probable pesticide illness from within and outside California, this episode ranks as the largest recorded North American outbreak of foodborne pesticide illness. In the past, intentional or inadvertent misapplication of aldicarb to cucumbers and mint was associated with similar, though more limited, outbreaks. The spectrum of illness reported in these outbreaks was similar to the current

one, ranging from mild to severe. No deaths have been reported from any of these food poisoning episodes.[6-8] In these cases, as with the 1985 watermelon epidemic, identification of the epidemic was dependent on alert clinicians who quickly recognized the symptoms and signs of carbamate pesticide poisoning and on the abilities of laboratories to identify aldicarb metabolites (a test not routinely performed when testing for pesticide residues). Without careful surveillance, it would be easy to overlook such an epidemic because of the nonspecific nature of symptoms of early cholinesterase toxicity.

Aldicarb has been implicated in at least two deaths in agricultural workers.[9,10] Although no deaths in this epidemic were attributable to ASO, the spectrum of clinical illness seen in this episode included many severely ill people. Some of the more serious symptoms and signs reported, such as marked bradycardia and hypotension, could have been lethal, particularly in the very young, the elderly, and the chronically ill. The prompt embargo and widespread publicity almost certainly were responsible for preventing a much larger epidemic and saving lives.

There are no known long-term or reproductive effects of aldicarb and its metabolites in the absence of maternal toxicity, and it is not a suspect carcinogen.[5,11]

One would expect that there would be a certain number of people in the state who had gastrointestinal illness onset coincidentally within 2 h of eating melon; hence, some of the sporadic cases were reported through September. However, underreporting at the beginning of the outbreak may have been substantial, given the long Fourth of July weekend and that the active surveillance system required 1 wk to implement fully. For example, the poison control centers were initially so overwhelmed with calls that they often did not have time to record complete reports; thus, many cases may have been lost to follow-up during the first week of the outbreak. However, a greater proportion of "probable" cases occurred after July 11; this suggests that a reporting bias in favor of minor coincidental illness may have occurred when the epidemic was first reported by the media.

It has been asserted that the entire epidemic was created by media coverage and reporting of illness coincidental with eating aldicarb-contaminated watermelons. However, the episode cannot be explained by coincidence. This is clear from the fact that those with laboratory-positive watermelons were likely to have a greater number of symptoms and more symptoms of severe acetyl cholinesterase inhibition than others.

A study of the geographic case distribution revealed no single retail source for contaminated melons, even when confined to cases confirmed with ASO-Positive tests in melons. This is probably due to the prevailing methods of distributing watermelons, which involve mixing unlabeled melons from numerous different sources. This results in marked intermingling during the distribution process. Any future outbreaks of illness related to watermelon will likely be difficult to trace using epidemiological information alone. This certainly suggests a need for better labeling or tracking methods for watermelons.

There were many illnesses clinically compatible with carbamate poisoning but associated with aldicarb-negative melons. Although, as mentioned above, some of these could have been coincidental occurrences, it is also possible that the laboratory analysis could not detect ASO at levels that can cause illness. This issue has implications for the regulation of pesticide residues in foods and deserves further study.

An outbreak of this explosiveness and magnitude could never have been investigated and documented without the full support and participation of California's local health departments, emergency departments, and poison control centers. The workload generated by this event in these institutions and CDFA is hard to quantify. CDHS has time accounting records that suggest thousands of person hours were devoted by one agency alone. Since the 1985 epidemic, California has begun an integrated food surveillance program that involves local health and environmental health departments, CDFA, and CDHS. Monitoring for pesticide-related illness uses a report form similar to the one used for the 1985 outbreak, but with the simpler case definition for a probable case of carbamate poisoning of diarrhea *or* nausea/vomiting within 2 h of eating produce. This case definition is easier to use in the field and has sufficient sensitivity (79%) so that any future outbreaks of consequence should not be missed, even though it will overlook one of five individual illnesses.

* * * * * * * * * *

Management of this epidemic involved hundreds of individuals in government agencies at all levels and at numerous private institutions. The authors thank all of these persons. Special thanks go to Harvey F. Collins, Ph.D., for his editorial assistance; to Barbara Hopkins, David Epstein, and Martha Harnly, who assisted with data processing and analysis and illustrations; and to Carolyn Harris and Gette Meneses, who typed the manuscript.

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References

1. Green MA, Heumann MA, Wehr HM, et al. An outbreak of watermelon-borne pesticide toxicity. Am J Pub Health 1987;77:1431–34.
2. U.S. Centers for Disease Control. Aldicarb food poisoning from contaminated melons - California. MMWR 1986;35:254–58.
3. Union Carbide Corporation. ALDICARB-FPD-WATER(a). Agricultural Products Co., Inc., Research and Development Department, P.O. Box 8361, South Charleston, West Virginia 25303. March 1980.

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4. SAS Institute, Inc. SAS/GRAPH user's guide. Cary, NC: SAS Institute, Inc., 1981.
5. Risher JF, Mink FL, Stara JF. The toxicologic effects of the carbamate insecticide aldicarb in mammals: a review. Environ Health Perspectives 1987;72:267–81.
6. Marshall E. The rise and decline of Temik (TM). Science 1985;229:1369–71.
7. Goes AE, Savage EP, Gibbons G, et al. Suspected foodborne carbamate pesticide intoxications associated with ingestion of hydroponic cucumbers. Am J Epidemiol 1980;111:254–60.
8. U.S. Centers for Disease Control. Suspected carbamate intoxications - Nebraska. MMWR 1979;28:133–34.
9. U.S. Environmental Protection Agency. Aldicarb information sheet. July 1985.
10. Lee MH, Ransdell JF. A farmworker death due to pesticide toxicity: a case report. J Toxicol Environ Health 1985;14:239–46.
11. Cambon C, Declume C, Derache R. Effect of the insecticidal carbamate derivatives (carbofuran, primicarb, aldicarb) on the activity of acetylcholinesterase in tissues from pregnant rats and fetuses. Toxicol Appl Pharmacol 1979;49:203–08.

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Goldman LR, Smith DF, Neutra RR, Duncan Saunders L, Pond EM, Stratton J, Waller K, Jackson RJ, Kizer K. 1990. Pesticide Food Poisoning from Contaminated Watermelons in California, 1985. Arch Environ Health. 45(4) 229-236.

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