Current Pesticide Issues in California - Michael O'Malley, M.D.

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Basic Concepts in Toxicology

Current pesticide issues in California

Assessing Dose

The truism in toxicology is that the "dose makes the poison". A similar principle applies in pharmacology when we think in terms therapeutic, sub-therapeutic, and toxic doses of drugs. However, for toxic substances, unlike prescription drugs, assessment of dose may be very difficult. We most often have imprecise information derived from our clinical histories and sometimes don't even know the precise nature of the chemical substances encountered by our patients. Fortunately, familiarity with common exposure situations greatly facilitates the task of history taking. This becomes clear when we ask about doses of common toxins such as alcohol or tobacco. How many beers did you drink last night? How many shots of whiskey? How many cigarettes do you smoke in a day? How many years have you smoked?

We also have laboratory measures of exposure - blood alcohol for measuring acute ethanol intake and urine cotinine for measuring exposure to cigarette smoke. Laboratory measures of dose are most often relative. They are useful because we have historical data associating a biological effect with a certain quantitative laboratory measurement - like a blood concentration of alcohol > 0.1% or 0.08%. Less often we can use laboratory data to quantitatively assess dose in absolute terms - as in the hypothetical situation when we have an acute exposure to compound x, followed by a 96 hour urine collection, knowing that excretion of the compound is 100% through the urine and is 50% compound y and 50% compound z. Measuring the amount of either y or z in the urine in this situation gives the original dose. Clinical exposure assessment is usually very imprecise compared to exposures measured in experimental settings, but is comparable to data derived from questionnaires, work histories, and other sources of information used in epidemiologic studies. Highly precise information on dose - from laboratory measurements or historical records - sometimes allows epidemiologists to assess the effects of spontaneous variations in dose. In the ideal situation this is termed a "natural experiment".

Dose-response - threshold vs. non-threshold effects

Response to a particular dose depends on the nature of the effect studied. In some biological symptoms there are clear threshold patterns of dose and response - indicating that no response at all occurs below a certain dose level as in the action potential

in the nerve axon. In other systems the dose response may be linear, sigmoidal or "sublinear", or rarely, exponential or "supralinear". Examples of threshold effects include response to chemical irritation of the eye and skin, detection of odor, chemical induction of birth defects, and various types of systemic poisoning. The existence of thresholds for the chemical induction of cancer is controversial, partially because of confusion about terminology. Some consider any deviation towards a sublinear response evidence for a threshold, while others seem to reject the idea of thresholds out of hand as an article of faith.

A set of interesting questions arises when considering the question of threshold vs. non-threshold responses in allergy mediated diseases. Classically allergic reactions demonstrate stereotypical patterns - hay fever, hives, asthma, and allergic contact dermatitis. These allergic reactions involve two possible thresholds - the initial dose(s) necessary to induce the allergy - and the lowest dose to which an individual reacts once sensitized. This concept is important since it points out that those likely to develop allergic reactions to chemical antigens are those with high dose rather than low-dose exposure. This classical model of allergy contrasts with theories proposed by "clinical ecologists" or "environmental allergists" who hold that certain people have immune systems altered by exposure to low levels of environmental chemicals and have become universally sensitive to synthetic chemicals.

Laboratory Benchmarks of Toxicity

In evaluating the toxicity of synthetic chemicals animal tests are commonly used as a means of predicting human toxicity. Even for acute effects these tests are not exact predictors of human response because of variations in species sensitivity to various chemicals and differences between human exposure patterns and the narrow set of exposure conditions used in standard toxicology tests.

LD50 studies These are commonly done with rodents, testing the dose required to kill 50% of an animal population following dermal, respiratory, oral, intraperitoneal, or intravenous exposure. The LD50 is actually a mathematical construct -read from a plot of dose (in mg/kg) vs. % mortality. Because it is easiest to administer the test compounds orally, the oral LD50 is the most common benchmark of toxicity. EPA, for

example, rates systemic toxicity of pesticides in terms of the oral LD50 as follows (<= 50 mg/kg - Category 1; > 50 mg/kg and <= 500 mg/kg -Category 2; > 500 and <=5,000 mg/kg - Category 3; > 5,000 mg/kg - Category 4.

Irritation studies

Based upon testing in albino rabbits, EPA rates eye irritation as follows: Corrosive; produces corneal opacity not reversible within 7 days - Category 1; corneal lesion reversible within 7 days, but causes persistent eye irritation - Category 2; No corneal opacities, irritation reversible within 7 days - Category 3; no irritation - Category IV.

Skin irritation is rated as follows: Corrosive - Category 1; Severe irritation at 72 hours - Category 2; Moderate irritation at 72 hours - Category 3; Mild or slight irritation at 72 hours - Category 4.

Cancer Bioassays

Animal cancer bioassays employ between 300 to 600 animals apportioned by sex and exposure into "high", "low", or no exposure categories. The high dose is chosen as the maximum dose that does not cause non-cancer mortality and therefore decreased survival - over the lifetime of the animal, about two years. The high dose chosen in this fashion is known as the maximum tolerated dose (MTD).

Historically, the use of bioassays has proven that potent animal carcinogens frequently turn out be human carcinogens: vinyl chloride, bis-chloro-methyl-ether (BCME), 4-aminodiphenyl (ADP), methylene- bis-(2-chloroaniline) MOCA or MBOCA. The extrapolation of the results of bioassays to low dose exposures is controversial. Standard regulatory practice is to use a linear extrapolation, but some industry groups have contended that technique is needlessly conservative. For example, data generated by the Chemical Industry Institute of Toxicology (CIIT), demonstrate what appears to be a non-linear dose response for nasal tumors induced by chronic inhalation of formaldehyde.

In evaluating animal test data described above it is important to remember that the results predict relative toxicity of humans to chemicals following acute exposures. Prolonged exposures may

lead to cumulative effects that are not predicted in acute toxicity tests. This phenomenon has been observed for both irritant effects and systemic toxicity.

Pesticides

Pesticides are chemical or physical agents that have biocidal properties. Classification may encompass either use or structural characteristics.

Use Classes include insecticides, fungicides, herbicides, molluscicides, and bacteriocides depending on the target organism. **Chemical classes** don't correspond to use categories but do give a general idea of mode of systemic toxicity. However, it is often difficult to difficult to predict local irritant or allergic effects on skin, eyes, or respiratory tract based upon chemical structure alone.

Use Categories versus Chemical Class Structure

Use Category	Structural Categories
Insecticides	Organochlorines, organophosphates, carbamates, pyrethrins, synthetic pyrethroids, nicotine, rotenone
Herbicides	Trichloro/dichloro-phenoxyherbicides, urea derivatives, carbamates, triazines, glyphosate
Fungicides	Carbamates, organophosphates, miscellaneous compounds including captan, captafol, pentachlorophenol, iprodione, elemental sulfur
Anti-microbials	Triazine-S-triones -chlorine releasing agents, chlorine, dichloronitrobenzene
Rodenticides	Coumadin and derivatives - long and short acting anticoagulants; strychnine; sodium fluoroacetate (compound 1080).

Common Modes of Exposure

The most important physical property of any chemical agent in terms of evaluating exposure is its vapor pressure. For materials with vapor pressure < 10^{-3} mm Hg, respiratory exposure is not very likely except when a fine aerosol is generated and remains airborne for a prolonged period of time. Even in pesticide application work, previous studies have demonstrated that dermal exposure accounts for 95-99% of the total potential exposure for most non-volatile pesticides as indicated in the following table below. Dermal exposure is the principal route of exposure for most field work. Ingestions are obviously infrequent in the work place, but have led to some serious poisonings on the job:

Vapor Pressures of some common pesticides

Material	Vapor Pressure - mm Hg
Phosphine	23,369
Sulfuryl fluoride	>760
Methyl bromide	1,725
Water	24
N-butyl mercaptan	83
Dichlorvos (DDVP)	$1x10^{-2}$
Mevinphos	$2x10^{-3}$
Malathion	$1.2x10^{-4}$
Chlorpyrifos	1.8x10-4
Chlordane	$1x10^{-5}$
Dimethoate	$8x10^{-6}$
Cynazine	1.6x10-9
Phosalone	$< 10^{-9}$

Distribution of Exposures in the California Work Force

Agricultural use of pesticides generates both direct and indirect exposures.

Direct exposures: mixers, loaders, applicators & flaggers.

Indirect exposure from pesticide residue on foliage and commodities; among fieldworkers highest exposure comes from hand work in close contact with heavy foliage (Grapes>Tree Crops>Row Crops). Degree of exposure depends on application history, compliance with reentry requirements, and breakdown of pesticide. Breakdown is very rapid with some compounds (phosdrin, dimethoate) and very slow with others (phosalone, guthion, chlorothalonil, propargite). Predicting the rate of breakdown is a key element in allowing safe use of most pesticides on field crops and also protecting consumers from excessive residues on food. Field workers are protected by waiting period know as **reentry intervals** and consumers by a related waiting period called a **preharvest interval.**

Non-agricultural use encompasses a whole host of exposure situations:

-household exposures - structural pest control, garden use, childhood exposures. Products of most frequent concern include insect sprays, household antibacterial agents, ant traps, rodenticides, insect powders, and herbicides.

-retail workers - indoor spills from pesticide containers, often with pesticide concentrates

-office/restaurant workers - residue of indoor applications

-outdoor workers - drift exposures

-emergency response workers - direct or indirect exposures to pesticide spills/drift

Illness Data

The relative possibility of serious illness following exposures to different portions of the work force can be ascertained by reviewing the distribution of probable and definite cases of organophosphate poisoning reported to CDFA through the Pesticide Illness Surveillance Program (PISP). Data in this system derive from workers' compensation reports (Doctor's First Reports - DFRs) and mandatory reporting of cases of pesticide illness by physicians (Figure 1).

The PISP data for probable and definite organophosphate poisoning were reviewed in order to ascertain cases that met a strict case definition (Figure 2). This review, in combination with employment denominators demonstrated that pesticide applicators (SIC 0721 -crop protection services) have by far the highest risk of illness (Figure 3). If cases are restricted to those meeting strict criteria for organophosphate poisoning, this single SIC code containing on average approximately 4,000 individual workers, has an illness rate 212 times higher than the rest of the California agricultural workforce and 4,451 times greater than the Non-agricultural work force. The rate of confirmed poisonings in this group from organophosphates alone is 64 times higher than the rate of systemic poisonings reported for the U.S. workforce as a whole $\approx$ 0.7 cases/10,000 workers employed (Figure 4). As shown in Figure 5, the leading causes of illness in the professional pesticide applicators are the Category 1 (LD50<=50 mg/kg) organophosphates, but Category 2 materials such as chlorpyrifos also make a contribution to the burden of illness. Many cases involve exposures to multiple Category 1 pesticides.

Focusing in on one category of illness and a single year's worth of data can of course be misleading. While pesticide applicators tend to have high rates of illness from year to year because of their direct exposures to pesticides, systemic illnesses in fieldworkers from systemic pesticide residue tend to be episodic. In years where no outbreaks are recognized the rates for systemic illness in fieldworkers may therefore appear to be zero. There were in fact two clusters of fieldworker illnesses associated

with the carbamate insecticide methomyl in 1988 - one due to a reentry violation and a second due to unexpected persistence of methomyl beyond the reentry interval. Neither episode appeared in our tabulation because the graph only depicted organophosphate associated illnesses. In 1987 there were three major clusters of fieldworker poisonings associated with the organophosphate phosalone, and these obviously did not show up in the data we looked at for 1988.

The episodic nature of illness among fieldworkers is a key to evaluating the reporting efficiency of California's surveillance program for pesticide illnesses. Since 1949 outbreaks of poisoning from organophosphate residue have been recognized in California, Oregon, and Washington.

Episode of Fieldworker Poisoning in California Since 1949

Year	Location	Chemical(s)	Crop	Number Ill
1949	Marysville	Parathion	Pears	20-25
1951	Delano	Parathion	Grapes	16
1952	Riverside	Parathion	Oranges	11
1953	Riverside	Parathion	Oranges	7
1959	Entire State	Parathion	Citrus	275
1961	Terra Bella	Parathion	Lemons	97
1963	Hughson	Parathion	Peaches	94
1966	Terra Bella	Parathion	Oranges	9
1966	Porterville	Parathion	Oranges	6
1966	Lindsay	Parathion	Oranges	3
1966	Navelencia	Parathion	Oranges	11
1966	Terra Bella	Parathion/ethion	Oranges	15
1967	Hughson	Azinphosmethyl/ethion	Peaches	23
1967	Ballico	Azinphosmethyl	Peaches	3
1968	Lindsay	Parathion	Oranges	19
1970	Porterville	Dioxathion/naled	Lemons	3
1970	Lindsay	Parathion/ethion	Oranges	2
1970	Terra Bella	Azinphosmethyl/ethion	Oranges	8-11
1970	McFarland	Parathion	Oranges	35
1970	Orosi	Parathion	Oranges	11
1971	Orange Cove	Parathion	Olives	8
1972	Lind Cove	Parathion	Oranges	3
1972	Exeter	Parathion	Oranges	9
1972	Huron	Parathion	Lettuce	4
1973	Fowler	Dialifor/phosalone/ethion /phosmet	Grapes	27
1974	Kerman	Azinphosmethyl/phosalone	Grapes	2
1975	Lemon Cove	Parathion	Oranges	16
1976	Fresno	Mevinphos	Lettuce	4
1977	Orange Cove	Parathion	Oranges	39
1978	Tulare	Ethion	Grapes	7
1980	Ballico	Azinphosmethyl	Peaches	6
1980	Salinas	Mevinphos/phosphamidon	Cauliflower	22
1981	King City	Mevinphos	Lettuce	41
1982	Strathmore	Parathion	Oranges	17
1982	Salinas	Mevinphos	Cauliflower	35
1982	Salinas	Oxydemeton-methyl	Cauliflower	17
1983	San Juan B.	Azinphosmethyl	Irrigating	2
1984	Firebaugh	Chlorpyrifos/acephate	Cotton	2
1985	Ducor	Parathion	Grapefruit	4
1986	Watsonville	Malathion	Strawberries	2
1986	Five Points	Methamidophos	Cotton	25
1986	Three Rocks	Methamidophos	Cotton	3
1987	Madera	Phosalone	Grapes	
1987	Madera	Phosalone	Grapes	
1987	Selma	Phosalone	Grapes	
1988	Delano	Methomyl	Grapes	

The reason for the episodic nature of fieldworker poisonings becomes clear upon examining a series of day-of-harvest samples looking at organophosphate residues collected by CDFA from 1975 to 1985 showed that only 174 (6.7%) of 2,563 showed detectable of the fields had detectable organophosphate residues, and 5 (0.2%) demonstrated residues that were considered hazardous. Although it is probably not safe to overgeneralize from this series of residue samples, they do indicate that exposures of fieldworkers to organophosphates is intermittent rather than continuous.

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Exposures to Household Pesticides

Exposures to pesticides in the home derive largely from the use of over-the-counter products, together with a smaller of exposures following treatments by professional structural pest control operators.

Deaths from Pesticide Exposure

A recent review of DPR files for deaths probably or definitely associated with pesticide exposure revealed thirty-two cases reported through our surveillance program between 1982 and 1987. Twenty-seven (84.3%) were attributed to non-occupational pesticide exposures. This group included twelve suicides, five accidental ingestions, and ten persons who entered fumigated structures prior to untarping.

There were five occupational deaths related to pesticides. Two were workers in a pesticide formulation plant who entered a tank containing residues of ethylene dibromide. A structural pest control worker received a fatal exposure to the solvent methylene chloride (a non-pesticidal ingredient of the mixture being sprayed) during application of a structural pesticide in a confined space. A security guard mistakenly entered a structure under fumigation. The final cases was a fieldworker who collapsed in a field recently sprayed with an organophosphate insecticide known as methamidophos. The last case is listed as probably related to pesticide exposure although there was evidence that the death may have been related to a cerebrovascular accident (stroke). However, due to complicated circumstances, a complete autopsy was not performed and no attempt was made at the post-mortem to evaluate blood cholinesterase.

Six additional deaths involving agricultural aircraft accidents were reported to the department from 1982 to 1987 for evaluation of a possible relationship to pesticide exposure. Four involved aircraft accidents in which no evidence of any pesticide exposure could be identified. These included one case in which pesticide exposure was ruled out at autopsy and three cases in which the plane which crashed carried no pesticide. Two aircraft accidents involved crop dusters carrying insecticides, but no definite evidence was found implicating the pesticide as the cause of the accident. As these data illustrate accidents involving agricultural aircraft do occur periodically in California. They are not usually related to pesticide exposures since the California Agricultural Code specifically prohibits agricultural

aircraft pilots from mixing or loading pesticides which they apply.

Two recent (1989 and 1990) deaths merit some discussion because of the unusual circumstances surrounding them. In December 1989 a structural pest control worker died during an application of a novel termite control pesticide employing liquid nitrogen. The underlying factors in this death were unusual construction techniques in the apartment being treated that allowed the gas to escape its normal confines, failure of the worker to wear required oxygen monitoring equipment, and the "solo" application of the asphyxiant gas, so that no one was on hand to rescue the applicator following his collapse.

In January 1990 an applicator died while applying parathion in a Kern County almond orchard. Although he had been well during the morning, he became symptomatic at 1 p.m., simply reporting to his supervisor that he didn't feel well and shortly there after became diaphoretic. He lapsed into unconsciousness without explaining what happened and died within 30 minutes of his first symptoms. Although the circumstances pointed to an accidental exposure, perhaps from a cleaning out a clogged spray nozzle, greater than 400 parts per million (ppm) of parathion were found in his stomach at autopsy. The rapid onset of symptoms is consistent with ingestion of parathion but the circumstances of exposure remain unclear.

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Systemic Poisons

Organophosphates

Classic hazard of agricultural employment.

Toxic to the nervous system by inhibiting the breakdown of the transmitter acetylcholinesterase by the enzyme acetylcholinesterase, resulting in overstimulation of portions of the nervous system which contain acetylcholine: post ganglionic fibers of the parasympathetic nervous system (control secretions of respiratory and GI tracts, heart rate, etc), sweat glands in the sympathetic nervous system, preganglionic fibers in the sympathetic nervous system, and skeletal muscle. The acronym MUDDLS is a helpful means of remembering the principal effects of cholinesterase inhibitors:

> Miosis (constriction of the pupils) Urination Diarrhea Diaphoresis (sweating) Lacrimation (tearing) Salivation.Other effects of note include bradycardia (slowing of the heart rate). This may be quite severe in some instances and may be responsible for episodes of dizziness and syncope (fainting) associated with organophosphate poisoning. These same symptoms may be produced by inhibition of acetylcholinesterase in the central nervous system, so that it is frequently impossible to ascertain the physiologic cause of the symptoms in individual cases.

Diagnosis is usually made based upon a history of exposure and a blood test of red cell and plasma cholinesterase. A test within the low normal range is not sufficient to rule out poisoning given the wide range of normal values in the population. In this situation, the diagnosis can be made by comparison with a baseline value, by doing serial followup tests, or by testing for regeneration of the native acetycholinesterase enzyme following in vitro treatment of a blood sample with the cholinesterase antidote protopam. There is no clear evidence as to what level of cholinesterase inhibition is necessary to produce symptomatic illness, although claims have been made for various thresholds (e.g. 50% depression, or 80% depression) in the past based upon different case series.

Recent examples: crew poisoning with phosdrin and phosphamidon in Salinas, 1980 following entry into a treated field 6 hours after application in order to band cauliflower. Serial cholinesterase testing demonstrated inhibition even in workers who initially presented with values in the low normal range.

1987 phosalone poisonings: slow absorption of moderately toxic compound over a one-two week period led to moderate to severe cholinesterase inhibition in 78 exposed individuals. This presentation is termed subacute given the relatively long asymptomatic period between first exposure and the onset of symptoms. The slow absorption also produced 21 individuals who were asymptomatic despite levels of cholinesterase depression comparable to that seen during the Salinas reentry poisonings. This episode also highlighted the necessity to recognize individual cases of fieldworker poisoning as sentinel health events.

Treatment: Atropine is an antidote for the muscarinic symptoms (respiratory and GI tract secretions, bradycardia, etc), but not for nicotinic effects (skeletal muscle) or on central nervous system effects. Atropine works by blocking muscarinic receptors and has a relatively short-lived effect. Protopam (2-PAM) is an adjunct to atropine and works by breaking down the enzyme-inhibitor complex. It is therefore effective against entire range of symptoms.

Carbamate Poisoning

This is qualitatively similar to organophosphate except that it is more readily reversible since the complex between the cholinesterase enzyme and carbamate insecticides readily breaks down. It is not necessary for new enzyme to be synthesized for normal functioning to be restored. Consequently it is more difficult to detect cholinesterase depression due to carbamates.

Treatment: Like organophosphates, carbamate poisoning may be treated by the use of intravenous atropine. However protopam (2-PAM) is of no value in treating carbamate poisoning, and may exacerbate the symptoms of poisonings with particular carbamates such as carbaryl and propoxur.Recent example:

1988 poisonings with methomyl in workers girdling grapes near Delano, California.

Fumigants

Prototype is the compound methyl bromide, which is a potent central nervous system toxin, most frequently following a respiratory exposure. Extremely high doses (2-3,000 ppm) produce acute loss of consciousness, respiratory depression and death. This pattern of anesthesia like effects is also typical of other fumigants such as sulfuryl fluoride. However, unlike sulfuryl fluoride, in the great majority of cases, the symptoms of overexposure to methyl bromide are delayed in onset. Most common initial symptoms in fatal or nonfatal cases with delayed onset are malaise, headache, visual disturbances, nausea, and vomiting. Later, a great variety of central nervous system manifestations appear, including numbness, ataxia, change of personality and seizures.

Organochlorines

DDT is the prototype organochlorine. It has low acute toxicity compared to toxic organophosphates; the oral LD_{50} in the rat is 113 mg/kg compared to the LD_{50} for parathion of 4-13 mg/kg. Symptoms of overexposure are most common after ingestion and include hyperexcitability, tremulousness, and in extreme cases, seizures. Most organochlorines are extremely persistent in the environment. They have an equally long half life in the body and can be measured several months after a significant exposure. A notable exception is endrin, which is much more readily metabolized (by oxidation) than the other organochlorines and is not detectable in the blood stream more than two weeks after an exposure. Endrin is two-four times more toxic than DDT, with an LD_{50} of 16-43 mg/kg in the rat. Food contamination with endrin has been responsible for a number of illness clusters worldwide. Because the symptoms resembled those of encephalitis, the cause of the illnesses was often not immediately apparent.

Aluminum Phosphide (Phostoxin®, Fumitoxin®)

Chemical and physical properties of phosphine:

Molecular weight: 34 grams/mole
Melting point: -133°C
Boiling point: -87.7 °C
Solubility in water: .26 cc in 100 cc H20

Reactivity

Reacts violently with halogen, halogen acids, nitric acid, nitrous oxide, and chromium oxychloride, silver and mercury nitrate, nitrogen trichloride, oxygen, and water. Corrodes copper, gold, and silver. Burns spontaneously in air at concentrations of 1.8% or greater if trace of P2H4 (diphosphine) present. Occupational Health Guideline (U.S. Department of Labor) also states that it reacts with halogenated hydrocarbons.

Odor threshold

Depends on contamination of aluminum phosphide preparation with other metal phosphides. Reported odor threshold ranges from 0.02 ppm to 1.5-3ppm.

Mode of Action

Probably cellular poison akin to cyanide, with cellular enzyme cytochrome oxidase affected, just as in cyanide poisoning.

Symptoms of Overexposure

Flulike illness: diarrhea, abdominal pain, headache, chest tightness, pulmonary edema. No specific laboratory abnormalities, but may cause liver enzyme abnormalities or elevated bilirubin; kidney dysfunction.

Exposure Limits

American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) is identical to current OSHA permissible exposure limit (PEL) of 0.3 ppm. Ceiling or short term exposure limit (STEL)=1 ppm. Documentation of TLV'S indicates that basis for phosphine TLV is study of Jones (American Industrial Hygiene Association Journal 25:376-379,1964) that found gastrointestinal symptoms (diarrhea and abdominal pain), headache, and chest tightness in association with exposures ranging from 0.4 - 35 ppm in grain handling workers. Maximum allowable concentration (MAC) in Europe is 0.1 ppm. Current TLV for hydrogen cyanide (HCN) by comparison is 5 ppm, the same as the ceiling limit. Cyanide TLV set on basis of slight symptoms associated with exposures ranging from 18-36 ppm and a safety factor below the levels producing these minor symptoms.

Protective Equipment

Exposures to PH3 above 10 ppm require self-contained breathing apparatus (SCBA). No respiratory protection required for normal use when applied outdoors.

Approved Methods of Disposal

Spent ash - small amounts of completely spent residual dust may be disposed of on site of application by burial or by spreading over the land surface away from inhabited buildings.

Spent ash should not be disposed of in dumpsters or other locations where confinement may occur.

Partially spent material (green ash) - disposed of using wet method, i.e. immersion in water or dousing with slurry of water and detergent.

Aluminum phosphide containers require triple rinsing prior to disposal as routine waste.

Fire Fighting Methods

CO2, dry chemical extinguishers
H20 and Halogen fire extinguishers not recommended. Water may exacerbate the fire. Effect of halogen (Halon®) extinguishers on fire uncertain. Occupational Health Guideline (U.S. Department of Labor) states that it reacts with halogenated hydrocarbons and thus might be expected to be made worse if freon extinguishers used.

Significant episodes with aluminum phosphide reported to the California Pesticide Illness Surveillance Program-1982-1990

1983

Index Case 2253-83; Priority investigation 89-LA-83: An explosion and fire occurred at a food processing plant in Los Angeles after the 700,000 cubic foot building was fumigated using 62 flasks with aluminum phosphide. Although the label recommended using three gallons of water/detergent slurry to deactivate each flask of fumigant, employees attempted to empty all of the flasks into a single 55 gallon barrel approximately half full of a water/detergent mixture. A sudden fire and explosion occurred after they emptied 22 flasks into the barrel. After they extinguished this initial fire, the two men dumped the remaining ashes into an empty barrel, shortly resulting in an even larger fire and explosion that took the fire department 30 minutes to distinguish. Exposed individuals developed nausea and headache, and several were hospitalized for observation.

1987

Case 165-87 - An employee of a Yolo county rice mill developed tightness in chest after aluminum phosphide ash he was disposing of in a 3/4 full 55 gallon drum ignited, exposing him to phosphine gas.

Cases 2206-87 and 2207-87: USDA quality inspectors complained of lightheadedness, and chest pain in conjunction with intermittent presence of phosphine odor at a Madera walnut processing operation. No air monitoring done at site despite complaints of inspectors. Medical records reviewed and telephone consultation conducted by Worker Health and Safety.

1988

Index Case 2334-88; priority investigation number 65-Tul-88: Sixteen workers became ill the day following fumigation of an almond sorting building in Tulare county, developing symptoms of nausea, headache, chest tightness, and abdominal cramps.

Index Case 2574-88; priority investigation 73-Ker-88: Episodes of conjunctivitis at an almond processing operation in Kern County. PH3 levels proved well below 0.3 ppm and did not appear related to the cause of the outbreak. Medical records and field investigation reviewed by Worker Health and Safety in conjunction with California Department of Health Services and Kern County Agricultural Commissioner's Department.

1989

Case 395-89: A forklift operator exposed to fumes inside rice mill warehouse after fumigation tarp ruptured February 28. He developed dizziness, vomiting, nausea, diarrhea, stomachache, disorientation, and decreased motor coordination for which he was seen at Kaiser Morse and UC Davis Occupational Medicine Clinic. A site visit was also made to the mill to evaluate the source of exposure and review the process for handling aluminum phosphide in the mill. Employer believed that exposure occurred after employee himself disturbed the tarp on palettes under fumigation.

Case 474-89: An unemployed male found dead in a rail grain car under fumigation with aluminum phosphide in transport from Texas.

Case 783-89: A rodent control worker in Los Angeles disposed of unspent aluminum phosphide pellets in a dumpster and second employee developed sore throat and chest tightness after putting out a subsequent fire.

Case 2664-89: An Alameda county electrician developed dizziness and difficulty breathing after putting out a fire in a dumpster caused by improperly discarded aluminum phosphide ash. Ash was residue of grain fumigation conducted by neighboring grain company on rail cars in transit.

1990

Cases 3004-90 and 3005-90: Unspent pellets of aluminum phosphide were improperly disposed of on February 21 at a Kern County almond processing operation by confinement in a tarped bin and subsequently exploded, injuring two employees - one with facial burns, hair loss, a broken left leg and perforated tympanic membranes (ear drums) and the second with facial burns and lacerations.

Index Case 842-90; Priority Investigation 27-Mad-90: Cotton debris piles at a generation plant, under fumigation with aluminum phosphide, broke out into flames. Six employees potentially exposed to phosphine from fire received medical examinations but had no symptoms. Draeger tube readings for phosphine taken at the site showed no detectable levels.

Methyl Bromide

A review of the medical literature indicates that fatal exposures to methyl bromide have occurred in association with blood bromide levels ranging from 50 to 400 ppm.[1,2] The air level of methyl bromide required to produce 120 ppm of blood bromide over an approximately 13 hour period cannot be estimated directly. The American Conference of Government Industrial Hygienists (ACGIH) set the current threshold limit value (TLV) for methyl bromide in occupational settings at 5 ppm to prevent pulmonary edema and

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[1] Hine CH. Methyl bromide poisoning. A review of ten cases. **Journal of Occupational Medicine.** 11:1-9,1969

[2] Bradford JC. Methyl bromide and related compounds. in Haddad LM and Winchester JF eds. **Clinical Management of Poisoning and Drug Overdose.** WB Saunders. Philadelphia, 1990; pp 1241-1243

serious neurotoxicity.[3] This standard derives from application of a safety factor to a Lowest-observable-effect-level (LOEL) in a study of workers who developed "mild systemic poisoning when exposed for two weeks to concentrations generally less than 35 ppm". From these data it seems likely that the breathing zone concentration of methyl bromide required to produce a fatality following a single thirteen hour exposure would significantly exceed 35 ppm. Although the human dose-response curve is not known with precision, animal studies do indicate that methyl bromide has a steep, sigmoidal dose-toxicity curve following short-term inhalation exposures,[4] with a relatively narrow range between exposures producing no observable effect and those producing a fatal outcome. It is plausible that the difference between less severe symptoms of the majority of those exposed to this compound and the fatal outcome of somes case derive from horter durations of exposure, varying concentrations of the gas, and the nature of the dose-response curve for acute inhalation exposures to methyl bromide.

Non-Systemic Illness

Eye injuries and skin disease make up about 2/3 of all pesticide related cases reported in California. Majority are related to irritant effects of the pesticides. For skin disease the most notorious irritant is the miticide propargite, which has been responsible for several recent outbreaks in crews harvesting nectarines and citrus. Many cases are also associated with the use of elemental sulfur. Sulfur is not a potent irritant, but it is used at extremely high dose rates and residue levels encountered in the field may be quite high. In application work, direct exposures to bare skin are likely to result in irritation, but this can be prevented fairly simply by wearing a shirt with long sleeves and gloves to protect the hands. Fieldworkers are also prone to allergic contact dermatitis, especially from fungicides such as benomyl, captan, and chlorothalonil. Numerous plant species may produce reactions on the skin which are indistinguishable from those produced by pesticides.

Treatment of contact dermatitis from pesticides resembles that for poison oak: topical steroid creams and antihistamines. Systemic steroids may be indicated in severe cases.

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[3] American Conference of Government Industrial Hygienists: Documentation of Threshold Limit Values and Biological Exposure Indices; ACGIH, Cincinnati, Ohio; 1986

[4] Hayes WJ. **Handbook of Pesticide Toxicology.** Academic Press. San Diego, 1991 p668-671

Pesticide Carcinogenicity

Recognition of individual cases of occupational disease frequently presents a diagnostic challenge, even when there is a short interval between exposure and the onset of illness. This is especially true in regard to pesticide exposures since the symptoms of poisoning are usually non-specific and resemble those of influenza and other common non-occupational illnesses. Much of the data on the potential chronic health effects of pesticides of therefore comes from animal toxicology studies.

Animal Data

The animal data on pesticide carcinogenicity identifies several as carcinogens in one or more animal species only at the MTD. The predictive value of these results for human exposures is unclear to many. Compounds in this category identified from the California Department of Food and Agriculture (CDFA) SB 950 data base include glyphosate (Roundup), bromacil (Hyvar), captan, ethoprop and others. Data for the herbicide bromacil are given in detail below:

> Oncogenicity in Mouse: 80 animals of each sex tested at each dose for 18 months on dietary concentrations of 0, 250, 1250, 5000 ppm. Increased number of liver tumors (adenomas and carcinomas) observed at the high dose in males only at the high dose. Doses above 250 ppm in this study were associated with a number of adverse effects including liver cellular hypertrophy and cellular necrosis, atrial thrombus, and aortic root necrosis.
>
> Oncogenicity in Rat: 36 animals of each sex tested at each dose for two years on dietary concentrations of 0, 250, and 1250 ppm. No oncogenic effect was observed in this study, but the number of animals in each test group was not adequate to detect an effect if present. Weight retardation was noted in animals at doses higher than 250 ppm.

Compounds identified as carcinogenic at doses below the MTD include ethylene dibromide (EDB) and chlordimeform (CDF). Data for chlordimeform are given below from a 1976 study reported by the registrant of chlordimeforms to CDFA:

> Oncogenicity in Mouse: 50 animals of each sex were fed chlordimeform in the diet at 0, 20, 100, and 500 ppm for two years. No increase in tumors was noted for the 20 ppm treatment group, but malignant hemangioendotheliomas were noted in both sexes at 100 and 500 ppm doses in approximately 50% and 75% of the treated animals respectively. No oncogenic effects seen in similar study on rats or dogs. The principal metabolite of chlordimeform, 4-chloro-toluidine (4-COT), had previously

been found to produce the same kind of vascular tumors in mice in a study at NCI.

Pesticides Rated as Animal Carcinogens

There is approximate agreement about pesticides that are animal carcinogens. The list given below derives from a recently published text on occupational medicine.

Animal Carcinogens

Alachlor
Amitrole
Benomyl
Captafol
Chlordane
Chlorthalonil
Daminozide
Dichloropropene
Dimethoate
Ethafluralin
Ethylene oxide
Igran
Maleic hydrazide
Methyl bromide
Orazylin
PCNB
o-Phenylphenol
Propoxur
Thiophanate-methyl
Ziram

Amitraz
Arsenicals
Cacodylic Acid
Captan
Chlordimeform
Cypermethrin
Diallate
Diclofop
Dinitramine
Ethylene dichloride
Folpet
Lindane
Methanearsonic acid
Mirex
Oxyfluorfen
Pentachlorophenol
Profluralin
Ronnel
Trifluralin

Aldrin
Azinphosmethyl
Captafol
Carbon tetrachloride
Chlorbenzilate
Cyromazind
Dichloropropane
Dimethipin
Dithiocarbamates
Ethylene dibromide
Glyphosate
Linuron
Methomyl
Monuron
Paraquat
Permethrin
Pronamide
Thiodicarb
Triallate

Human Epidemiologic Studies

Human studies on the carcinogenicity of pesticides have been somewhat inconsistent, with results that have varied somewhat according to geography and from study to study. There have been many studies, for example, demonstrating increased risk of leukemia and hematopoietic cancer among farmers in the Midwest. The risk has been variously attributed to pesticides (specifically the herbicide 2,4-D) and other possible causes such as oncogenic viruses. For our purposes it will be of value to review specifically relevant data from California.

California

In California, the principal finding of mortality studies of agricultural workers has been a significant increase in the occurrence of non-malignant respiratory disease, which was observed by Carlson (Carlson, M.L., Petersen, G.R.: Mortality of California agricultural workers. J Occup Med 20(1):30-32, 1978 and again by Stubbs (Stubbs, H.A., Harris, J., Spear, R.C.: A proportionate mortality analysis of California agricultural workers, 1978-1979. Amer J lndus Med 6:305-320, 1984). The possible link between leukemia and lymphoma mortality and farm residence in California has also been explored, but no significant relationship could be demonstrated (Fasal, E., Jackson, E.W., Klauber, M.R.; Leukemia and lymphoma mortality and farm residence. Amer J Epidemiol 87:267-74, 1968). The California agricultural industry differs significantly from that in the Midwestern U.S. in the relatively small contributions made by grain and livestock production and the heavy production of specialty crops. It is uncertain whether the increased mortality from non-malignant respiratory disease is related to a chemical exposure or some other factor in the work environment.

The studies described above do not indicate any consistent increase in malignancies associated with agricultural employment.

Childhood Cancer and Pesticide Exposures

Case-control studies of childhood cancer have frequently used rather broad use categories to identify exposures, so they have been unable to associate particular pesticides with the positive findings. For example, pesticide exposures were positively associated with childhood brain cancer in Baltimore between 1965 and 1975 when compared to children without cancer, but not when compared to controls with other types of cancer (Gold, E., Gordis, L., Tonascia, J., et al.: Risk factors for brain tumors in children. Amer J Epidemiol 109(3):309-319, 1979). A study of childhood leukemia in Los Angeles reporting a positive association with pesticide exposures used only one control population (children without cancer selected by random digit dialing), so that it was not possible to easily assess the importance of recall bias (Lowengart, R.A., Peters, J.M., Cicioni, C., et al.: Childhood leukemia and parents' occupational and home exposures. J Nat Can Inst 79(1):39-46, 1987).

Childhood Cancer Clusters and Pesticide Exposure

Background

A cancer cluster, or cancer outbreak, can be defined as an increase in the number of cancer cases beyond that statistically predicted (based on appropriate regional or national cancer rates) for a given community within a specified period of time. This type of event is also known as a time-space cluster. This designation distinguishes it from clusters which are defined only geographically (space clusters). Space clusters are more perhaps simply identified as geographic areas where one or more types of cancer is persistently found to occur at a higher than expected rate for the entire period of time for which cancer incidence data is available.

Clusters may consist of a single tumor type, but clusters involving multiple tumor types are also frequently reported to public health officials. There is some theoretical reason to include the multiple tumor type outbreaks in the cluster definition since some carcinogens, such as vinyl chloride, are known to produce more than one type of primary cancer. However, in any cluster caused by a single agent, it would be expected that one or two types of cancer would predominate. Workers exposed to vinyl chloride, for example, show increased risks for biliary and liver cancer, brain cancer, and respiratory system cancer; however, the excess risk is far greater for liver and biliary cancer (more than 1,000 times the number of expected cases), than for brain (five times the number of expected cases), or respiratory cancer (twice the number of expected cases).

The most frequently hypothesized causes of community cancer clusters reported in the literature have been infectious agents, usually conceived as a slow acting virus, or a toxic environmental exposure. The infectious theory was popular in the 1960's and early 1970's, but none of the investigations reported in the literature succeeded in identifying a causal agent. Currently, most cluster investigations involve searching for a toxic environmental agent. The concern for toxic environmental agents perhaps derives from occupational carcinogens, such as bis-chloro-methyl-ether and vinyl chloride, which were first identified as the result of cancer cluster investigations. Although agents for a few occupational clusters have been identified and have proven to be of real significance, there has been no comparable success in identifying agents for space-time clusters of cancer in residential communities. Unique environmental agents have been identified for certain space clusters, where cancer has been identified as an endemic, rather than epidemic, problem. In the Cappadocia region of Turkey, for example, two villages have been identified with high incident rates for mesothelioma; environmental investigation has demonstrated that an asbestos-like mineral, known as zeolite, is common in the region.

McFarland

The California Department of Health Services and the Kern County Health Department have extensively studied the problem of cancer in McFarland, which was identified by concerned parents of children with cancer. The phase I study, conducted by the Kern County Health Department during 1985 and 1986, identified an approximately three fold excess of childhood cancer in the 11 year period from 1975 to 1985. The cancer types in the ten cases identified included fibrosarcoma, large cell lymphoma, neuroblastoma, rhabdomyosarcoma, leukemia (two cases), osteogenic sarcoma, Wilms' tumor (2 cases), and astrocytoma. The phase I investigation also demonstrated an increase in increase in adverse reproductive outcomes (fetal deaths, stillbirths, and low birth weights) was also identified for the period 1981 to 1983. Exposures were evaluated by taking soil, air, and water samples during the investigation. These did not reveal any ongoing problem with chemical environmental pollutants, but could not rule out of a transient exposure occurring at an earlier date as the cause of either the cancer cluster or the cluster of adverse reproductive outcomes. Besides chemical exposures, the Phase I environmental study also demonstrated the absence of greater than background levels of ionizing radiation. Interviews with Voice of America officials (VOA) regarding the VOA transmitter near Delano revealed that the transmitter used shortwave radiation for broadcasts to South America. The VOA records of shortwave radiation were being reviewed by the state Department of Health Services at the time the phase I study was written, but were expected to show that levels of shortwave exposures in McFarland were similar to that of the general U.S. population.

Phase II studies at McFarland were completed by the California Department of Health Services in 1988 and included review by a

panel of outside experts. The investigation focused on questioning parents of cancer cases and controls (children who did not have cancer) to see if there were any significant differences in previous illnesses, medications, exposure to x-rays, type of housing, exposures to pesticides or other chemicals, and amounts of water consumed. One finding of interest in the phase II study results regarded parental employment. 80% of the fathers of cancer cases, compared with 45% of the fathers of controls, stated that they had worked in the fields in the time interval between three months before pregnancy and the date of diagnosis of the child's cancer. This finding was perhaps attributable to recall bias, since the information apparently derived from an open-ended question, which the "case" fathers may have filled out more completely than "control" fathers.

Environmental exposures evaluated during phase II included review of well water data from six wells supplying the community, especially regarding levels of nitrate contamination. Pesticide use reports were also reviewed to determine which pesticides were used most frequently between 1980 and 1982, the period in which a single exposure could have conceivably accounted for the bulk of the cancer cases and also the cluster of abnormal reproductive outcomes. This review did identify eight pesticides which were used more frequently than in 1979. Of these eight compounds, only four (dimethoate, fenbutatin oxide, dinoseb, and dinitrophenol), were used in substantial volume. No evidence was found indicating that any of the cases had been either directly or indirectly exposed to these materials.

Rosamond

The town of Rosamond is located in southeast portion of Kern county, on a high desert plateau near the Edwards Air Force Base. The population in 1980 was 2,878 with 898 school age children. Data from the Environmental Epidemiology and Toxicology Section of CDHS demonstrate indicate that eight cases of childhood cancer (ages 0-19) occurred in during the years 1975-1984. In Rosamond, 1.47 cases of childhood cancer would have been expected to occur during this time. The statistical probability that 8 cases would occur in a town the size of Rosamond is two in a thousand. Four of the cases were noted to be medulloblastoma, a rare childhood tumor which arises in the brainstem and cerebellum (posterior cranial fossa), a rate of occurrence 20 times that expected. It is not primarily an agricultural community, but there are 4 manufacturing plants in the Rosamond area and a number in surrounding areas. One of the plants is a metal smelter and was considered by CDHS as a possible source of community pollution with toxic metals and also dioxins from the plant smokestacks.

Reproductive Effects of Pesticides

Birth defects from exposure to environmental chemicals are generally considered to be threshold phenomena - i.e. no effect

will be noticed below a minimum dose - and many teratogens only that cause birth defects at doses also associated with maternal toxicity. It is also reassuring that descriptive epidemiologic studies have shown that there is no general increase of birth defects in farm the San Joaquin Valley compared to urban areas of the state.[5] There is nevertheless cause for concern because of the high risk of systemic poisoning in agriculture relative to the remainder of the work force some exposures may exceed the threshold or safe-dose.

Thirty-five workers became ill after they entered a cauliflower field contaminated with residues of three different insecticides, the organophosphates oxydemeton-methyl (Metasystox®), mevinphos (Phosdrin®), and a carbamate, methomyl (Lannate®). One crew member was pregnant with a 4-week old fetus. At birth, the 3200-g female infant had multiple cardiac defects, bilateral optic nerve colobomas, microopthalmia of the left eye, cerebral and cerebellar atrophy, and facial anomalies. The cardiac defects included ventricular and atrial septal defects, stenosis of the pulmonary artery, and a patent ductus arteriosus. The child died at 14 days of age. There was no family history of birth defects, nor any maternal risk factor present, except that doxylamine (Bendectin®) had been prescribed at 9 weeks fetal age. It was unlikely that doxylamine was responsible for the observed anomalies. Of the three chemicals involved, reproductive effects in test organisms have been observed only with oxydemeton-methyl. This case represents the first report of human malformations associated with prenatal exposure to this chemical. Further studies may be warranted to determine if a causal relationship exists.[6]

Background on Contact Dermatitis and Occupational Skin Disease

Clinical Description - Contact Dermatitis is a common condition, found in about 2% of the population surveyed by the National Health Assessment Nutrition and Examination Survey (NHANES). The hallmark of this condition is the correspondence between the pattern of dermal exposure to the agent in question and the distribution of subsequent blistering and erythema, followed by cracking, fissuring, and lichenification. Depending on injury to melanocytes in the basal layer of the epidermis, acute episodes may have sequelae of either hyper- or hypopigmentation.

Mechanisms of Injury - Contact dermatitis is most commonly produced by **direct irritation**, arbitrarily differentiated from a skin burn (e.g. acid on the skin) only by the difference in intensity and acuteness of the irritant response. At the other

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[5]Birth Defects in California: January 1, 1983 to December 31, 1986. A report of the California Birth Defects Monitoring Program, January 15, 1990

[6]Romero P, Barnett PG, and Midtling JE (1989): Congenital anomalies associated with exposure to oxydemeton-methyl. **Environmental Research** 50:256-261

end of the spectrum are weak irritants (or low concentrations of potent irritants) that produce a response only after repeated exposure. This type of **cumulative irritation** to the skin thus produces contact dermatitis just as cumulative repetitive trauma to the skeletal system produces stress fractures and tendonitis. The classic example of this is hand dermatitis produced by wetwork - characterized by drying, cracking and fissuring of the hands following a period of weeks or months of repeated contact with water, detergents, or solvents. An important variation of direct irritation is **phototoxicity** - skin irritation produced by a UV or visible light activated chemical - e.g. 8-methoxy psoralen.

Allergic contact dermatitis is usually a delayed hypersensitivity (Type 4 immune response) reaction that develops after repeated exposures to an antigenic substance. Once the sensitivity develops, an acute response - identical to that produced by irritant contact dermatitis - may recur following exposure to very small doses of the antigen. This exquisite sensitivity is identified clinically by use of the patch test - a provocation test that uses a concentration of the suspected allergen too low to produce an irritant response when occluded against the skin for 24 hours. The appropriate concentration for testing must be worked out by a tedious trial and error procedure, but fortunately this has already been done for common allergens such as nickel, neomycin, rubber additives, preservatives, etc, found in the household environment. Important subtypes of allergic contact dermatitis include **photoallergic contact dermatitis** and **contact urticaria**. In the former condition, the initial chemical exposure produces no response until an antigen is produced by interaction with UV or visible sunlight. Many reactions to sunscreens containing para-amino-benzoic-acid (PABA) are of this type. Contact urticaria is a unique syndrome characterized by a Type 1 rather than a Type 4 allergic response to dermal exposure - so the skin findings are the evanescent wheal and flare reaction rather than the persistent vesiculation and erythema produced by the type 4 reaction.

Differential diagnosis - Contact dermatitis has been confused (both under and over diagnosed) with nearly every type of skin condition. However, the most common conditions to consider in the differential diagnosis include seborrhea, atopic eczema, psoriasis, superficial fungal infection (tinea of the hand, trunk, foot, etc), pityriasis rosea, polymorphous light eruption, drug eruptions, and heat rash (miliaria rubra).

Occupational Skin Disease

Skin disease is the most common form of occupational illness, accounting for approximately 1/3 of all occupational disease reported. Besides contact dermatitis, which accounts for 90% of all cases, it includes skin infections, and a variety of less common conditions such as occupational acne and chemical leukoderma (vitiligo provoked by exposure to an exogenous

chemical agent). Recognition of the condition may be difficult since the differential includes non-occupational contact dermatitis as well as the long list of skin conditions that mimic contact dermatitis. It is helpful to question patients about the type of work they do and the materials that come into direct contact with the skin. If you can ascertain the pattern of dermal exposure that occurs on the job, you can move the diagnosis of occupational skin disease higher or lower on your list, depending upon the degree of correspondence you see with the lesions you observe. Remember that some agents readily penetrate work clothing, so that you may see reactions in apparently non-exposed areas of skin. Dusts, for example, collect in the flexural areas and around the cuffs of long sleeve shirts, and around the collar line, producing a typical pattern of flexural eczema very difficult to differentiate from atopic dermatitis.

High risk groups to consider in terms of occupational skin disease include agricultural workers (plants and agricultural chemical exposures), construction workers (cement, poison oak), machine shop workers (cutting oils), and rubber workers (a whole variety of rubber additives). A variety of case examples will be discussed focusing on outbreaks of skin disease in several of these high risk groups.

Treatment

Treatment of contact dermatitis is straightforward, employing use of topical (valisone, lydex, etc) and systemic steroids. Supportive treatment with moisturizing creams (Eucerin, lubriderm, etc) is very important, particularly in cases of irritant contact dermatitis. It may be necessary to treat cases with extensive areas of skin involved like burn patients, and a portion of these cases may require hospitalization for intensive nursing care.

Pesticides and Occupational Skin Disease

Statistical information on dermatitis derived from workers compensation sources can be imprecise, but is useful in conjunction with a knowledge of the literature on occupational skin disease. In the sections below, statistical information on the distribution of skin disease in the California agricultural workforce is presented, followed by a review of available literature on pesticides and occupational skin disease, and finally a summary of some recent outbreaks among California agricultural workers.

Illness Statistics on Skin Disease in Agricultural Workers

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ILLNESS STATISTICS[7]

[7]Adapted from O'Malley MA and Mathias CG: Distribution of Lost-work-time Claims for Skin Disease in California Agriculture; Am J Ind Med 14:715-20,1988

INTRODUCTION

National statistics have consistently identified agriculture (among manufacturing, construction, services, retail trade, etc) as the major industrial division at the highest risk of occupational skin disease (Wang, 1979; O'Malley, 1988). In order to develop specific priorities in the control of occupational skin disease in agriculture, we evaluated the distribution of claims, by source of skin disease, among the subdivisions of agricultural employment. The study was limited to California agriculture because of detailed employment information which was available for that state (California Employment Development Department, 1978, 1979, 1980, 1981, and 1983). Although agriculture in California, with its heavy concentration of specialty crops, is not typical of agriculture elsewhere in the U.S., its workforce is well worth studying per se, since it accounts for approximately a third of the total U.S. Agricultural employment (U.S. Bureau of Labor Statistics, 1984).

RESULTS

2,722 claims for lost-work-time skin disease among 2,355,802 employees of California agricultural businesses were reported to the SDS file during the study period (11.5 cases/10,000 employed). Limited demographic information in the SDS file showed that claimants were 77.6% male, and ranged in age from 14 to 84 years, with a median age of 27.8 years. Fewer than 3% of claimants were less than 18 or more than 64 years of age. Denominators to match the demographic information available for the cases were not available, so that claims rates by age and sex could not be calculated.

In the overall workforce cases were most frequently attributed to plants (52.1%), chemical exposures (20.4%), and food products (12.5%), with a "miscellaneous" and "nonclassifiable" causes accounting for most of the remaining cases (15.0%). Among the subdivisions of agriculture considerable variation occurred in the distribution of cases by source of exposure (Table 1). For skin disease associated with plants the forestry subdivisions (SIC's 081, 082, 084, and 085) had the highest rate of claims (53.5 case/10,000 employed), and this group notably had no reported cases due to any other source of exposure. Other groups with elevated claims rates (given as cases/10,000 employed) for plant-associated skin disease included SIC 078-Landscaping Services (35.9), SIC 018-Horticultural Specialties (15.9), SIC 071-Soil Preparation Services (9.9), SIC 029-General Livestock Farms (9.6) and SIC 027-Animal Specialties (7.6).

In addition to having an elevated rate of claims from plant dermatitis, Horticultural Specialties had the highest rate of claims associated with exposure to agricultural chemicals (5.1 cases/10,000 employed). Other groups with elevated claims rates (given as case/10,000 employed) in this category included SIC 072-Crop Services (4.7), SIC 025-Poultry and Egg Production (3.8), SIC 016-Vegetables and Melons (2.8), SIC 019-General Crop Farms (2.5), and SIC 071-Soil Preparation Services (2.5).

DISCUSSION

Although compensation claims clearly represent only a sample of the actual cases (Discher, 1975; Kahn, 1976), they represent an invaluable population based data source which gives us one of the few clues we possess as to which groups of agricultural workers are at highest risk of skin disease. While it would be desirable to assess the distribution of skin disease based on a complete set of cases, our previous work has demonstrated that the distribution (or ranking) of groups at high risk for occupational skin disease is relatively independent, across a fairly wide range, of the magnitude of case reporting rates (O'Malley, 1988). Misidentification of the true distribution of skin disease from claims data is only possible where the degree of underreporting varies substantially from one SIC group to the next. Claims rates can thus serve as a first step in developing descriptive data on the epidemiology of agricultural skin disease. As with other types of descriptive data, these rates are primarily of value in setting priorities for disease prevention efforts, and in generating hypotheses which can be followed up by analytical studies and improved surveillance techniques.

Within each SIC classifying cases by source of illness has clear descriptive value. The results shown in Table 1 give an interesting perspective, for example, on the relative role of plants and food products versus the role of chemicals in causing skin disease in the major subdivisions of agriculture. In the forestry subdivisions (SIC's 081, 082, and 085) plants were associated with all claims filed for lost-work-time during the study period, with the vast majority undoubtedly related to poison-oak (Baginsky, 1982). In the Horticultural Specialties group (SIC 018), plants were identified as the source of the majority of skin disease cases, but chemical exposures also played a significant role. For the Crop Services group (SIC 072), chemical exposures appeared to be the predominant source of skin disease, while in the Vegetables and Melons (SIC 016) the majority of claims derived from exposure to food products. Even the fairly limited information on the source of illness contained in the SDS file (O'Malley, 1988) can thus be of value when cross-classified with the product-oriented SIC code.

For SIC subdivisions with skin disease associated with two or three major sources of skin disease, proper classification of cases may be a significant problem in the SDS data. In the Horticultural Specialties group (SIC 018), for example, one can postulate that cases of skin disease due to contact with plants are sometimes attributed to chemical exposures and vice versa. Since many of the crops (e.g. primrose, chrysanthemums, daisies, lilies, and poinsettias) produced in the industry and the chemical compounds it uses (e.g. benomyl, dienochlor, chlorothalonil, and captan) are recognized sources of allergic contact dermatitis (Cronin, 1980a; Cronin, 1980b; California Department of Food and Agriculture, Worker Health and Safety Branch: 1978, 1979, 1980, 1981, 1983; van Joost, 1983; Johnson,

1983), skin patch testing would appear to be the only means of satisfactorily identifying the source of individual cases in Horticultural Specialties workers. Although the results of such specific medical tests are not contained in the SDS file, the data in the file and existing information on important exposures in the industry do suggest that a series of systematic patch test investigations into these cases would be worthwhile.

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Table 1

Distribution of Skin Disease in California Agriculture by SIC group+ and Source of Exposure

SIC Group	Employed++	Agricultural Chemicals: Cases	Rate#		Plants: Cases	Food Products: Rate#	Cases	Total Rate#	Cases	Rate#
011 Cash Grains	26,538	2	0.8		8	3.0	0	0.0	12	4.5
013 Non-Grain Cash Crop	135,401	22	1.6		22	1.6	2	0.1	58	4.3
016 Vegetables/Melons	258,492	72	2.8		96	3.7	122	4.7	366	14.1
017 Fruits/trees/nuts	603,615	138	2.3		354	5.9	76	1.3	652	10.8
018 Horticulture	125,826	64	5.1		200	15.9	6	0.5	324	25.7
019 General Crop Farms	290,856	74	2.5		98	3.4	28	1.0	248	8.5
021 Non-dairy Livestock	34,877	4	1.1		14	4.0	2	0.6	24	6.9
024 Dairy Farms	61,669	8	1.3		6	1.0	0	0.0	36	5.8
025 Poultry/Eggs	41,670	16	3.8		6	1.4	6	1.4	48	11.5
027 Animal specialties	10,571	0	0.0		8	7.6	0	0.0	12	11.3
029 General Livestock	10,375	0	0.0		10	9.6	0	0.0	10	9.6
071 Soil prep services	8,046	2	2.5		8	9.9	0	0.0	12	14.9
072 Crop Services	177,246	84	4.7		34	1.9	34	1.9	186	10.5
074 Veterinary Services	48,931	0	0.0		0	0.0	0	0.0	4	0.8
075 Non-vet anim. serv.	24,309	2	0.8		2	0.8	0	0.0	6	2.5
076 Farm Labor Services	354,669	60	1.7		144	4.1	52	1.5	304	8.6
078 Landscaping Services	127,655	8	0.6		394	30.9	0	0.0	404	31.6
081 Timber Tracts	478	0	0.0		0	0.0	0	0.0	0	0.0
082 Forest Nurseries	37	0	0.0		2	541.0	0	0.0	2	541.0
084 Gathering Forest Prod	76	0	0.0		0	0.0	0	0.0	0	0.0
085 Forestry Services	2,026	0	0.0		12	59.2	0	0.0	12	59.2
091 Commercial Fishing	11,862	0	0.0		0	0.0	0	0.0	0	0.0
092 Fish Hatcheries	481	0	0.0		0	0.0	0	0.0	2	41.6
097 Hunting & Trapping	66	0	0.0		0	0.0	0	0.0	0	.0
Total	2,355,802	556	2.4		1,418	6.0	748	3.2	2,722	11.6

* Based on cases reported to the U.S. Supplementary Data System (for 1978, 1979, 1980, 1981, and 1983) by the California Department of Industrial Relations from tabulations of Employers' First Reports of Occupational Injury or Illness. All cases involved one or more lost workdays, listed by Standard Industrial Classifications (SIC) as used in Standard Industrial Classification Manual, 1972; with 1977 supplement; the Statistical Policy Division, Office of Management and Budget. ++Employment figures are derived from unemployment insurance records by the California Employment Development Department. Reported figures are the sum of mid third quarter employment (peak agricultural employment) for the study period. # Rates are reported as number of cases/10,000 workers employed.

Table 2*

Pesticides associated with Skin Disease

*from O'Malley MA, Mathias CG, and Coye MJ: Epidemiology of Pesticide Related Skin Disease in California Agriculture: 1978-83; in Dosman Ja, Cockroft D (eds): Principles of Health and Safety in Agriculture. Boca Raton, CRC Press, 1989, pp 335-338

in California Agriculture PISP[9] Data 1978-1983

Pesticide	Cases	Percent of Total
Propargite	241	18.7
Sulfur	195	15.1
Glyphosate	53	4.1
Propargite/Sulfur	51	4.0
Methyl bromide	43	3.3
Benomyl	30	2.3
Captan	26	2.0
Petroleum products	24	1.9
Cyhexatin	21	1.6
Captan/sulfur	18	1.4
Dinitrophenol	18	1.4
Ethylene dibromide (EDB)	15	1.2
Paraquat	15	1.2
Methomyl	13	1.0
Diazinon	12	.9
Ziram	12	.9
Captafol	11	.9
DD mixture	11	.9
Chlorothalonil	10	.8
Dicofol	10	.8
Captan/DCNA/Sulfur	9	.7
Acephate	8	.6
Carbaryl	8	.6
Dichloronitroaniline (DCNA)	8	.6
Malathion	8	.6
Naled	8	.6
Dienochlor	8	.6
Triadimefon	8	.6
Dimethoate	6	.5
Fenbutatin oxide	6	.5
Anilazine	5	.4
Benomyl/captan	5	.4
Maneb	5	.4
Simazine	5	.4
Metam-sodium	5	.4
Zineb	5	.4
Other	168	13.0
Unknown	184	14.3
TOTAL	1,288	100.0

[9] Pesticide Illness Surveillance Program (PISP) operated by the California Department of Food and Agriculture; all reported cases are included in published PISP reports, regardless of the amount of time lost from work.

Reporting period excludes cases from 1982.

Literature on Pesticides and Occupational Skin Disease

In this section the literature on pesticides and occupational skin disease is reviewed, presented by use categories of pesticides, with particular emphasis on the materials associated with occupational skin disease in California agriculture (Table 2).

Fungicides

Many of the synthetic chemicals compounds which produce skin reactions in agricultural workers are fungicides. Compounds discussed below include elemental sulfur, benomyl, dyrene, captan, difolitan, chlorothalonil, and the thiocarbamates.

Elemental Sulfur

The large number of cases associated with elemental sulfur in California agriculture (Table 2) is striking and would seem to imply that sulfur is a potent skin irritant. However, standard skin irritation studies for most agricultural formulations have shown just the opposite.[11] Other work, using guinea pigs[1], has shown that a 25% concentration of wettable powder produces a 2+ irritant reaction. In the same study, the guinea pig maximization test, conducted with a 5% topical concentration of sulfur-[1], has shown that elemental sulfur is a moderately strong experimental allergen. Two case reports implicate elemental sulfur as a human contact allergen. Schneider[2] reported two cases of contact allergy in patients who used medications containing elemental sulfur to treat superficial fungal dermatoses. Both patients had positive patch test reactions to 5% elemental sulphur in various vehicles. A control series was not reported.

Wilkinson[3] reported the case of a professional gardener with a previous history of atopic eczema who developed an eczematous eruption involving the elbow flexures and the right hand. He had a positive patch test reaction to 5% sulphur in petrolatum,but a control series was not reported. Gregorczyk and Swieboda[4] described 15 cases of desquamative dermatitis among 425 Polish

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[11]Unpublished CDFA data

sulphur miners in which irritant dermatitis due to elemental sulfur may have played a part.

These disparate pieces of information suggest that an active irritant may be formed from elemental sulfur by oxidation (sulfuric acid) or reduction (hydrogen sulfide). A reaction to a mixture containing sulfur in an agricultural formulator is discussed below.

During October, 1988 a 41 year old man was using a sulfur/malathion/carbaryl mixture to dust roses for powdery mildew. During the application he was wearing a short sleeve shirt and some of the dust accidentally contaminated his right forearm. Since the day was quite warm, he was sweating profusely and the material stuck to his arm. Four hours later he experienced some burning and itching. The following morning when he took a shower the irritation was worse and he then noticed a rash on his forearm. He had no history of asthma, hay fever, eczema, or other previous skin condition. The remainder of his past medical history was unremarkable and he was taking no medicines at the time of the incident.

At the time of examination, there was a punctate pattern of contact dermatitis over the right forearm. The opposite arm was unaffected. The patient declined any medication and the rash resolved without sequelae two weeks later. He declined to be patch tested to either sulfur, malathion, or the specific mixture which he had been using. He was able to resume handling the dusting sulfur without problem provided he wore a long sleeve shirt in order to prevent the dust from directly contacting the skin.

Comment This case report demonstrates that sulfur can produce irritant dermatitis given sufficient exposure. Given the short interval between the exposure and onset of the dermatitis, there is little likelihood that the reaction is allergic rather than irritant. This is also suggested by the absence of a recurrent dermatitis when he resumed using dusting sulfur wearing protective clothing.

Benomyl (Benlate®)

Benomyl is a systemic carbamate fungicide with extremely low potency as a cholinesterase inhibitor, used in the control of many diseases of fruits, nuts, vegetables and ornamental plants. Guinea pig tests of benomyl for irritancy conducted by the manufacturer at 12.5% and 25% aqueous dilutions were reported to be negative.[5] But the maximization test conducted in the same test showed 2% benomyl to be a potent experimental allergen. The first report implicating benomyl as a contact allergen appeared in 1972. Seven Japanese women employed in a greenhouse by a carnation grower developed dermatitis of exposed skin after benomyl was sprayed there on two occasions. No cases occurred until two weeks after the second spraying. The seven patients had 2+ reactions to a 1:10 dilution of benomyl in olive oil and three control subjects were negative.[6] van Ketel[7] also reported a case of benomyl sensitivity, confirmed by patch testing (with a 1% preparation which elicited no reaction from 10 controls), in a begonia grower. A second report from the Netherlands by van Joost also highlighted the occurrence of benomyl hypersensitivity in nursery workers and florists.[8]

The above cases illustrate the capacity of foliar residues of benomyl to cause allergic contact dermatitis in nursery workers.

Zweig et al[9] demonstrated that exposure up to 5.4 mg/person-hour to benomyl is also a potential problem in strawberry harvesting. Everhart[10] studied benomyl applicators and noted a maximum total exposure of 26 mg of benomyl in mixing/loading operations, and markedly lower total exposures associated with field residue exposure (12 mg), and home use of the material (<1 mg). Hargreave[11] noted the possibility of exposures from handling treated commodities, demonstrated persistent benomyl residues on litchi nuts up to 15 days after postharvest treatment in a dipping process: 20 ppm of benomyl in skin and 1.3 ppm in the flesh of the nut.

Captan

Captan is a fungicide commonly used on grapes, apples, almonds, and other crops. It is formulated as a wettable powder, dust and flowable powders - alone or in combination with other fungicides and insecticides. In addition to use as a pesticide, it has been used successfully as a treatment for pityriasis versicolor.[12] Jordan and King found a 5% sensitization rate to captan using a modified Draize test on volunteer subjects, and a 10% sensitization rate on volunteers using captan in the human maximization test. Women appeared to become sensitized more frequently than men.[13]

Captan has been reported to cause dermatitis in association with apple spraying in Scandinavia[14] and has been a relatively frequently reported problem in California (Table 2). A series of 178 patients at the Nagoya City University Medical School who were routinely tested between 1977 and 1980 with the North American Contact Dermatitis Research Group of standard allergens. 5.6% had significant positive reactions to captan. No clinical details were given in the report, but the surprisingly high percentage reacting to captan, presumably, an uncommon exposure, raises the possibility that the material cross reacts with other allergens in the standard series.[15] Rudner[16] observed a similar high percentage of captan reactors in the North American Contact Dermatitis Group results in 1976 and speculated that results might be due to cross reaction with thiurams.

Captafol (Difolatan®)

Captafol has a chemical structure nearly identical to that of captan,and has many similar uses as a fungicide. Captafol accounted for 62 (28.7%) of a series of 274 cases of pesticide associated contact dermatitis seen in Japan between 1968 and 1970.[17] In a similar series of 18.2% of 121 Korean farmers likewise reacted to the material.[18] Cottel observed several cases in San Joaquin Valley orchard farmers in 1972 with positive patch test responses to a .1% aqueous preparation of captafol.[19] Irritant and allergic contact dermatitis was also seen in 23% of 133 New Zealand timber workers tested with the material by Stoke.[20] Camarasa found 4 of 7 ill workers from a captafol packaging plant had 3+ patch test responses to 1% captafol.[21] An outbreak of dermatitis due to captafol sensitivity was also seen among a group 36 workers on a Kenyan coffee plantation.[22] Urticaria and asthma were part of the clinical picture reported affecting 7 (17.1%) of 41 workers in a captafol packing operation in a chemical shed.[23] The similar occurrence of asthma and contact dermatitis in a welder employed by a maintenance firms which serviced captafol distribution plants was reported by Groundwater.[24] Captafol thus apparently is capable of causing both delayed and immediate types of hypersensitivity as well as irritant dermatitis.

Plondrel® (diethyl-phthalimido-phosphothioate)

Plondrel is a fungicide that structurally resembles captan and captafol, but is dubbed an organophosphate because of its phosphothioate group. In 1975 van Ketel[25] reported the cases of in two culturists and two florists who sprayed Plondrel® on roses

and subsequently developed dermatitis. All four reacted to 0.1% Plondrel® in petrolatum, but no reactions occurred in twenty control subjects tested with the same material. van Ketel subsequently reported a third case of hand eczema in a 21 year old florist who had a 3+ reaction to 0.1% plondrel.[26]

Dyrene (anilazine)

Dyrene is a fungicide, formulated as a wettable powder, commonly used on tomatoes and a wide variety of other crops. Its chemical structure somewhat resembles the triazine herbicides with two of the alkyl groups replaced by chlorine atoms. The only report of dyrene sensitization in the medical literature appeared in 1980-

describing an outbreak of dermatitis among 14 of 26 workers on a single farm in Tennessee. Of seven workers patch tested with .1% dyrene 6 had positive reaction and no reactions occurred among 9 unexposed controls.[27,28] This compound has also been noted as a cause of contact dermatitis among agricultural workers in California (table 2). An earlier series of cases was reported in more detail

Chlorothalonil

Chlorothalonil (tetrachlororisopthalonitrile, a substituted benzene derivative) is a broad spectrum fungicide which has widespread use on ornamental flowers and other crops. A case of allergic contact dermatitis from chlorothalonil in a cabinet maker was first reported in 1980.[29] An outbreak of dermatitis due to chlorothalonil sensitization was subsequently reported in a group of Norwegian wood treatment workers by Johnsson in 1983. Fourteen of twenty workers interviewed had complaints of suspected to be work related contact dermatitis. On testing with 0.01% chlorothalonil, 7 demonstrated allergic reactions, 6 were negative, and one had a reaction reported as "toxic".[30] A series of three nursery workers with allergic contact dermatitis due to chlorothalonil was reported by Bruynzeel and van Ketel, and included one patient who reported attacks of generalized pruritus and urticaria.[31] All of the reports described above employed patch tests of 0.01% chlorothalonil in petrolatum because higher concentrations proved irritating in control subjects tested.

Cases of contact dermatitis associated with exposure to chlorothalonil have been relatively frequent (table 2), but it is uncertain how many cases are due to irritant versus allergic mechanism. The value of patch testing in suspected cases of chlorothalonil dermatitis is demonstrated by the case described below.

Contact Urticaria in a Conifer Seedling Nursery

Three illness reports were received during 1988 by the Humboldt County Agricultural Commissioner's (HCAC) office regarding dermatitis and hay fever symptoms among employees of a conifer seedling nursery in Korbel, California. Ill employees of the nursery were interviewed and examined during the site visit to

ascertain the previous history of atopic illness and recent history of allergic illness. Results of investigations conducted by the State Compensation Insurance Fund and the Humboldt County Agricultural Commissioner's Office were also reviewed for information regarding the history of illness and the results of environmental sampling. The nursery which employs four to five full time employees and approximately fifteen seasonal workers (nursery helpers and lead workers) from December to June. There are 15 enclosed greenhouses on the property and 5 shade frames where seedlings are raised under less controlled conditions. Total output from the nursery is 3.5 to 4 million seedlings/year. The two principal products are coast redwood (Sequoia sempervirens) and Douglas Fir (Pseudotsuga menziessi). Other products include Western White Pine (Pinus monticola) and Eucalyptus seedlings.

The affected employee is a 48 year old woman employed at the nursery since 1976, and has worked as both a lead person (full time worker) and nursery helper (seasonal). She has no past history of atopy except a history of "whelps" which she has developed after taking penicillin. While at work on November 14, 1988 she developed a very acute swelling of the eyelids, accompanied by nasal congestion, watery eyes, itching of throat and cough. Examination by a local physician episode indicated that she had marked facial edema and also rales and wheezing in the left lower lung fields. The problem was present intermittently thereafter when she was at work, but usually cleared in the evenings. It was also better during the weekends when she did not work and during periods of vacation or layoff. At the beginning of February, 1989 she had a very acute episode of facial swelling while she was driving a forklift which cleared within 2 hours after she was removed from the work environment.

During February 1989 she was sent to the patch test clinic at UC San Francisco. She had a negative reaction to the standard patch test tray, which includes the fungicide captan, but does not contain any of the other pesticides to which she had potential exposure in her work. She showed an immediate hypersensitivity reaction to both redwood and Douglas fir seedlings which were taped to her skin for 20 minutes. Since both seedlings had apparently been previously treated with fungicides it was not possible to ascertain whether the reaction was to the plant material <u>per se</u> or possibly to fungicide residue on the leaves. Followup patch testing at UC San Francisco with untreated seedlings again demonstrated positive reactions typical of

contact urticaria. She again showed no reaction in an open patch test to captan, but showed an "anaphylactoid reaction" to chlorothalonil. Application records showed that this material had been applied to any of the greenhouses at the nursery since early December, 1988. However, chemical analysis revealed that significant concentrations of chlorothalonil were nevertheless present on all three seedlings tested. No detectable levels of other pesticides which had been applied at approximately the same time period could not be detected. The environmental persistence of this compound would appear to be an important reason for its effect on this particular patient. A description of the clinical findings in this case was recently published by Dannaker and Maibach.[32]

Thiocarbamates

This group of fungicides structurally resemble the rubber accelerator disulfiram (Antabuse®), a common sensitizer present in the U.S. standard patch test series.[33] The entire group of compounds - ethylene bisdithiocarbamates (EBDC's) - has become the focus of regulatory concern because of metabolic conversion to the carcinogen ethylene thiourea (ETU). ETU is also recognized as a skin sensitizer and may be the active allergen in the EBDC pesticides.[34]

Maneb and Zineb

Maneb is a common name applied to manganese ethylene bisdithiocarbamate, a widely used fungicide for tomatoes, fruits,and a number of field crops. It is marketed under the several brand names including Dithane M-22 and Maneb-80. Its chemical structure resembles that of thiram and it is closely related to zineb (zinc ethylenebisdithiocarbamate and a number of other thiram-like compounds used as fungicides worldwide. Matsushita[35] tested maneb and zineb experimentally with the guinea pig maximization procedure and found both compounds to be potent sensitizers with a high degree of mutual cross reactivity. Concentrations of 5% or more were found irritating.

In 1977 Burry reported two cases of sensitization in seed handlers from South Australia. He obtained positive patch tests with .5% of a mixture of maneb and zineb known as Mankobunt.[36] Cases of sensitization to EBDC's were also reported in large

series of contact dermatitis cases patch tested in Korea and Japan as well as cases reported to public health departments in Great Britain.[37]

Exposures sometimes occur in floral shops. Nater[38] reported three cases of sensitization from workers handling ornamental plants in the Netherlands. Two were office workers who had purchased Maneb spray to care for the plants in their office, and the third was a 51 year old woman who worked as an assistant in a flowershop. Rudzki and Napiorkowska[39] reported a similar case of a woman florist who was sensitized to a pesticide mixture (Sadoplon 75) containing the fungicide tetramethylthiuram disulphide(thiram)-whose structure resembles that of maneb and zineb. An earlier case due to environmental exposure on a golf-course was reported by Shelley.[40]

Dichloronitroaniline (DCNA, Botran®)

DCNA is a material used on grapes to protect against the effects of Botritis and other fungal pathogens. Although it has not been reported in the medical literature as a sensitizer, its chemical structure resembles that of known potent sensitizer, dinitrochlorobenzene, and some of the cases associated with DCNA in California (Table 2) may be due to allergic contact dermatitis.

Pentachlorophenol (PCP)

PCP is a broad spectrum biocide capable of causing serious systemic toxicity. In addition to these systemic effects, it is capable of causing chloracne as well acute dermal irritation.[41] Exposures are principally associated with its use as a wood preservative and fungicide.

Creosote

Used to preserve railroad ties and telephone poles, creosote is derived from either coal tar or petroleum pitch and has a number of well studied affects on the skin. Coal tar products,including creosote, have complex effects on the skin,ranging from irritation to phototoxic effects to the induction of skin cancer. A large outbreak of dermatitis due to creosote was reported in 1943: 450 of 2700 wood treaters,roofers, and carpenters examined by Jonas showed evidence of creosote induced burns and skin

irritation. Individual case reports have linked creosote with skin cancer.[42]

Insecticides

Organophosphates

These insecticides are the classic cause of occupational poisoning in agricultural workers. Rycroft has noted that despite the lack of clinical reports describing organophosphate associated skin disease, many organophosphates are potent experimental sensitizers.[43]

Malathion

This widely used compound controls a variety of insects from aphids to mosquitoes. It has numerous preparations which are used on orchards, ornamentals and row crops. Its low toxicity is due to the fact that mammalian carboxy esterases quickly detoxify malathion after absorption.[44] Milby[45] showed that 1% and 0.5% solutions of malathion were sensitizing in human volunteers.

Malathion has infrequently been a cause of occupational illness.[46,47,48] The only survey of skin sensitivity due to malathion yet conducted was reported by Milby.[35] The patch tested one hundred fifty seven poultry workers with 1% aqueous solution of technical grade malathion and found 4 with positive reactions. All four had high exposure to malathion and three had a history of recent skin eruptions suggestive of undiagnosed malathion contact sensitivity. In a survey of poultry workers two of forty three had positive patch test reactions to malathion and had histories of undiagnosed skin ailments. It was considered possible that the active sensitizer in the malathion preparations used in the above studies could have been a contaminant of technical malathion, diethyl fumarate. Some of the skin reactions associated with malathion currently being reported (Table 2) may be secondary to allergic contact dermatitis.

Diazinon

Diazinon is an organophosphate of relatively low toxicity which serves to control soil insects;many pests of fruits,vegetables

and ornamental plants; and is also used as a seed treatment. No documented reports of contact allergy to diazinon have appeared in the medical literature, but it has been reported to have a moderate capacity as a skin irritant.[49] Collins et al reported a case of porphyria cutanea tarda associated with exposure to diazinon;[50] a possible mechanism for this effect was subsequently identifed by the same group of authors, who noted experimentally that the isodiazinon isomer of diazinon is capable of inhibiting the liver enzymes ferrochelatase and coproporphyrinogen oxidase.

Naled

Naled is an organophosphate of relatively low toxicity which is used on a variety of crops as a preharvest treatment and for control of flies in poultry sheds. Contact sensitization to naled has been reported in workers employed by a chrysanthemum grower after twelve of them had entered chrysanthemum beds recently treated with Naled and dicofol. Those workers who were patch tested to both compounds had 3+ responses to naled and no reaction to dicofol.[51]

Dichlorvos (DDVP)

Dermatitis associated with DDVP was first noted in dogs and cats wearing DDVP containing flea collars.[52,53,54] Persistent papular dermatitis was reported by Mathias[55] in the case of a truck driver who had accidental skin contact with DDVP while transporting a commercial formulation of the material. Patch tests with 1% and 0.1% DDVP in Petrolatum were both negative.

Methyl Parathion

Bhargava et al[56] noted the case of an Indian woman with no prior history of illness who developed erythema multiforme, with typical iris lesions following exposure to 2% methyl parathion sprayed to kill bedbugs. Skin biopsy was consistent with the diagnosis of erythema multiforme and the lesions were reproduced upon challenge with "methyl parathion in the form of snuff".

Pevny[57] reported a 40 year old West German vineyard worker with dermatitis of the hands, forearm, and face who had positive patch test reactions to 7 of 27 pesticides to which she was tested, including parathion, methyl parathion, metasystox®, methathione, azinphosmethyl, EDTA, and pyrethrin. All seven materials were

used in the vineyard where she worked and she developed an additional iatrogenic sensitization to the organochlorine pesticide fentichlor.

Carbamates

Carbaryl

Carbaryl is a broad spectrum insecticide used to control insects on more than 100 crops. The only report of dermatitis associated with carbaryl came from Kenya where an applicator applying carbaryl was reported to develop a rash after spilling a solution of carbaryl and occluding the material against his skin for several hours.[58] In the large series of cases of contact dermatitis due to pesticides reported by Lee, there were no cases of sensitivity to carbaryl among the 121 cases tested.

Vapam-metam sodium

A soil fumigant and nematocide, metam sodium is also effective against weeds and soil fungi. Cases of contact dermatitis associated with metam sodium have been reported principally from the Germany where cases of irritation or sensitization from this material in the production of root vegetables appears to be common.[59,60,61]

Miticides

Propargite (Omite®)

Propargite is a widely used pesticide, formulated as a wettable powder (Omite® 30W) that is effective against many different species of mites infesting citrus, stone fruit, grapes, grapes, strawberries and many other crops. It is frequently combined with sulfur to form a miticide/fungicide combination.

In a survey of 121 laborers with dermatitis from a rural clinic in Korea(26), one had contact dermatitis and a history of exposure to propargite (Omite) which coincided with a positive patch test reaction. None of the remaining patients reacted to the material. This is virtually the only evidence that propargite might be a sensitizer. Extensive experimental work

with both animals and humans has demonstrated that propargite is a potent dermal irritant.[62]

An outbreak of poisoning and dermatitis with Omite occurred in Japan in 1970. After the miticide was used on some orange trees, 40 of a group of workers developed irritant dermatitis and 43 of the 47 had signs of non-cutaneous effects - principally irritation of the respiratory tract.[63] Dermatitis experienced by California mixers and loaders in 1979 and 1980 led to the development of water soluble packaging for propargite, first used on a trial basis in the San Joaquin Valley in 1981.[64] This formulation has apparently reduced, but not eliminated dermatitis from propargite in mixer-loaders of pesticides (Table 2). Outbreaks of dermatitis associated with exposure to propargite have also been noted in California field workers. Extremely high exposures to propargite (ranging from 0.89 to 5.49 $\mu g/cm^2$) followed application of a new formulation known as Omite® CR and were associated with an outbreak of severe dermatitis in Tulare County citrus harvesters 1986.[65] A subsequent outbreak of somewhat milder dermatitis associated with the Omite® 30W formulation and median exposures of 0.61 to 0.69 $\mu g/cm^2$ was reported in 1988.

Dermatitis in Stone Fruit Harvesters

In June, 1988 the Department of Food and Agriculture, Worker Health and Safety Branch, received a report regarding an outbreak of dermatitis among three crews of nectarine harvesters in Tulare County, California. On interview, 42 (80.7%) of 57 workers in the three affected crews reported experiencing a rash between June 13 and June 27. Rashes reported on questionnaire were found to be contact dermatitis on medical examination in 42 (91.3%) of the workers. No cases were reported among members of a comparison crew employed by the same grower and none were identified on examination. Significant negative associations were noted between rash reported on questionnaire and exposure to formetanate hydrochloride, B. thuringiensis, environmental heat, and work in untreated orchards; positive associations were noted for exposures to propargite and iprodione. The results of skin examinations performed on June 27 and 28 demonstrated a similar pattern of association between the rash score for individual workers and exposures between June 13 and June 27. Although exposures to iprodione and propargite were highly correlated and could not be separated on multivariate analysis, only 34 (74%) of the reported cases were preceded by exposure to iprodione whereas

all of the cases were preceded by exposure to propargite. Propargite was thus the only exposure which could have accounted for all of the reported cases and also had a positive association with the occurrence of dermatitis. Contact dermatitis in the present episode was associated with levels of dislodgeable propargite residue ranging from 0.55 to 1.91 ug/cm^2, with median values for the three affected crews equal to 0.61, 0.64 and 0.69 ug/cm^2 respectively. Median residue to which the unaffected crew was exposed during the same time interval was 0.15 ug/cm^2.

Cyhexatin (Plictran® - Tricyclohexyl hydroxystannate)

Cyhexatin is an organotin compound used as an acaricide-miticide to control plant feeding mites resistant to other pesticides. It is formulated as a wettable powder. Contact allergy due to this material was reported in 2/121 patients from a clinic population in rural Korea. An additional patient had a history suggestive of plictran sensitization but had a negative patch test. Other organotin compounds[66,67] have been reported as skin irritants and it is plausible that cyhexatin is also somewhat irritating. This compound was removed from the market in 1988 secondary to adverse reproductive effects observed in animal tests.

Herbicides

Bipiridiyls (Paraquat and diquat)

Paraquat and diquat are contact herbicides and dessicants with a wide variety of applications in weed control and treatment of seeds. Dermal application of paraquat under occlusion has produced skin irritation in rabbits at doses of 1.56 mg/kg of the ion. The LD50 is 24 mg/kg when applied experimentally to rabbit skin but this can be reduced to 4.5 mg/kg if the paraquat is applied under occlusion.[68] It is evident from these and other experimental studies that paraquat produces injury by irritation and corrosion of the skin rather than by sensitization. Paraquat has frequently been reported as a cause of skin injury in Great Britain where it is available as an over the counter preparation for home use,[69] and has also caused numerous cases of occupational eye injury.[70]

Paraquat is a potent systemic toxicant and was reported to cause fatal injury on absorption through the skin of a 39 year old

woman who regularly mixed batches of paraquat in her work. She developed ulcers of the upper and lower extremities after contaminating several scratches on her arms and legs with paraquat. These ulcers failed to heal over a period of four weeks and subsequently progressed to respiratory failure over a period several weeks, the only documented case of skin exposure leading to fatal paraquat poisoning.[71]

Glyphosate (Roundup®)

Glyphosate is an isopropylamine derivative of glycine-used as a non-selective post-emergence herbicide to control perennial grasses, broadleaf weeds plus many tree and woody brush species. It has no cholinesterase inhibiting activity. Technical grade glyphosate has been shown to be non-reactive in skin and eye irritation studies on file with CDFA, but the 39% formulated product causes moderate levels of irritation, a disparity probably due to irritant properties of surfactant(s) in the latter. Virtually all of the cases of eye, skin, and respiratory irritation reported in California have occurred in applicators of the formulated product, and the residue is not known to produce any sort of skin reaction. In the CDFA series, cases of skin irritation associated with glyphosate were often associated with contaminated work clothing occluding the material directly against the skin. A phototoxic reaction to a preservative present in Roundup® was reported by Hindson and Diffey.[72]

Phenoxy and Urea herbicides

2,4,5-T and 2,4-D are both derivatives of phenoxyacetic acid but are produced by different processes. While production of 2,4,5-T has been associated with numerous outbreaks of chloracne,[73] no such association has been made for 2,4-D. Chloracne, attributable to contamination with tetrachloroazoxybenzens, has also been associated with the production of urea herbicides such as diuron.

Fumigants

Dichloropropene-Dichloropropane mixture

This product was used as a soil fumigant-nematocide until its manufacture was discontinued by the Dow Chemical company. The dichloropropene component is still available under the trade name

Telone®. Contact sensitization to dichloropropane has been reported,[74] but the material is rated as a primary irritant and most skin reactions to the material are probably due to this effect.
Dichloropropene caused illness in 46 persons exposed in a trucking accident near Yuba City in 1975. The most common symptom was mucous membrane irritation, although a number of victims had chest tightness and non-specific signs of systemic poisoning. The material has elsewhere been reported to cause edema, redness and necrosis of the skin.[75]

Methyl bromide

A fumigant and nematocide used for agricultural and structural pest control. An industrial accident in 1942 revealed the capacity of methyl bromide to cause skin burns and irritation.[76] Methyl
bromide can readily be absorbed through the skin[77] and has been responsible for a number of serious occupational poisonings in California.[78] Other fatal poisonings are reviewed by Hayes(74).

Ethylene dibromide (EDB)

This was removed from the market because of concern regarding its carcinogenicity in 1983 and controversies about safe levels in consumer products. 16 cases of skin burns and minor irritation occurred in California workers exposed to ethylene dibromide in 1975-76. Each of the burns resulted from a failure of prompt decontamination.[79] One fatal ingestion of EDB has been reported,[80] and in 1982 two California workers died after entering a storage tank containing the material. Skin necrosis was a prominent feature at autopsy in both cases.[81]

Plant Dermatitis

Plant dermatitis is usually in the differential diagnosis of occupational skin disease and for some agricultural SIC's plant dermatitis is the principal form of occupation skin disease (Table 1). A current reference on the subject has been published by Benezra et al;[82] an exhaustive older reference (currently out of print) was published by Mitchell and Rook.

Pesticides and Occupational Skin Disease - Michael O'Malley, M.D.

Two outbreaks of dermatitis were investigated during 1988 and 1989 which proved to be associated with exposure to toxic weeds rather than to pesticides. The first involved a crew of approximately 10 workers engaged to pull weeds in a cotton field near Firebaugh, California during July, 1988. On July 27 several workers noted the onset of dermatitis on legs and forearms and subsequently sought medical treatment. Eight of nine workers examined by CDFA on August 3 showed residuals of a severe dermatitis over the thighs and forearms. Weed samples taken from the implicated field on August 3 were identified by a CDFA botanist as cocklebur (Xanthium pennsylvanicum), field bindweed (Convolvulus arvensis), and thorn apple (Datura stramonium). Chemical residue samples taken from the field were somewhat contradictory. A residue sample taken August 2 showed 53 ppm of propargite, approximately equivalent to 0.19 micrograms/cm^2 of dislodgeable residue. A sample taken August 5 showed no detectable propargite. Application records indicated that no pesticides had been applied to the field during 1988.

The second outbreak involved a crew of workers pulling weeds in a sugar beet field near Willows, California during May, 1989. Fourteen cases of bullous contact dermatitis were identified among 42 crew members. The grower's pesticide application records revealed that no pesticides had been applied to the field since November 1988 and no pesticides were present on tested samples of sugar beet foliage. The principal weed identified in a botanical survey of the field was Mayweed (Anthemis cotula), but other species were also noted, including cocklebur (one of several Xanthium species), and prickly lettuce (Lactuca scariola). Experimental patch testing with A. cotula in a volunteer subject demonstrated its capacity to produce skin irritation. Irritant reactions to A. cotula were felt to be the probable cause of the observed outbreak of contact dermatitis in the fieldworkers.

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EMERGENCY MEDICAL MANAGEMENT OF PESTICIDE POISONING

Kent R. Olson, MD, FACEP

I. IMMEDIATE MANAGEMENT: PRE-HOSPITAL

A. SCENE SAFETY & PROTECTIVE GEAR

- **Most products are highly contaminating.** The potential for secondary contamination of rescuers is significant, and critical medical care may have to wait until victims are decontaminated or rescuers are properly protected.
- **Skin protection needed for most products.** Most organophosphates, carbamates, and chlorinated compounds are well-absorbed across the skin, and even after initial decontamination rescuers are advised to wear 1-2 layers of latex gloves and use disposable gowns or aprons.
- **Respiratory protection mainly for solvents.** Most pesticides are not highly volatile, but their solvents (such as xylene) are readily vaporized and may pose a significant inhalation hazard to rescuers working in enclosed or poorly ventilated areas (eg, the ambulance).

B. PATIENT EXTERNAL DECONTAMINATION (This should be performed by properly protected rescuers working in the decontamination area before the victim is transferred to less-protected personnel in the support area.)

- **Strip contaminated clothing.** Contaminated clothing should be double-bagged and labelled.
- **Copious water flush.** This is usually performed with the victim standing in a "kiddie" pool or laying on a gurney or backboard over a diked or otherwise contained area to catch water runoff. Routine wash is 10-15 minutes if victim's condition allows.
- **Soap & shampoo wash.** Especially useful for oily or otherwise adherent materials on skin or in hair. Any mild soap (eg, hand dishwashing soap) is fine.

C. PREHOSPITAL MEDICAL CARE (To be performed only after victim decontamination in the hot zone.)

- **Airway & Breathing.** Hopefully, the victim's airway and breathing are intact after the necessary delays in decontamination. Remember that the main cause of death in pesticide poisoning is respiratory failure.
- **Atropine.** If OPs or carbamates are involved, atropine may be appropriate and is carried on all paramedic rigs. Administer a test dose of 0.5-2 mg; if the patient rapidly develops dilated pupils, tachycardia, dry and flushed skin, etc, it's unlikely to be a serious anticholinesterase intoxication. In contrast, serious poisonings may require several hundred mg of atropine.

Remember that atropine does not reverse skeletal muscle weakness, the primary cause of respiratory arrest and death.

- **Do not induce emesis.** The possibility of abrupt onset of seizures or coma makes this too dangerous. If the paramedics carry activated charcoal, it may be given (50 gm PO) if the patient is awake and cooperative.

II. HOSPITAL DIAGNOSIS & TREATMENT

A. PREVENT STAFF & FACILITY CONTAMINATION

- **Assure on-scene decontamination.** This is the most important measure since it may prevent serious contamination of hospital facilities and personnel as well as ambulance providers.

- **Prepare reception & treatment area.** Prepare an area just outside the ED entrance for a quick inspection for adequacy of decontamination, with soap, shampoo, and warm water hose for additional decon if necessary. Also useful for the unexpected, still-contaminated arrivals.

- **Protective gear for staff.** If adequate decontamination has been carried out at the scene, hospital staff should need no special precautions other than gloves and disposable gowns. On the other hand, unexpected or improperly decontaminated victims may arrive. Therefore, it's a good idea to keep water-resistant aprons and extra gloves for skin protection, and to maintain an outdoor reception and decon area so that inhalation of solvents does not occur.

  It is not reasonable to expect ED staff to be fitted, trained, and repeatedly drilled in use of specialized respiratory protective gear such as gas masks and SCBA.

B. REASSESS ABCs

- **Airway.** Suction excessive secretions, and intubate the trachea if necessary.

- **Breathing.** Recognize that respiratory muscle weakness may abruptly lead to respiratory paralysis. Check ventilatory function with bedside spirometry and arterial blood gases.

- **Circulation.** Hypotension is not common with OPs, carbamates, or chlorinated hydrocarbons, unless another complication such as seizures or ventilatory failure has occurred. Arrhythmias may occur, especially with chlorinated compounds owing to myocardial sensitization.

C. ANTIDOTES (Anticholinesterase agents)

- **Atropine.** Effective for muscarinic symptoms and signs (salivation, sweating, bronchorrhea, bradycardia, abdominal cramps) but not nicotinic effects (muscle weakness). See prehospital care above for dosage/use.

- **Pralidoxime.** More specific "antidote" which reverses binding of the OP to cholinesterase; it reverses both muscarinic and nicotinic signs. Administer 1-2 gm IV over 5-10 minutes, and repeat as necessary every 4-12 hours as needed. Recent studies suggest that a constant infusion (approximately 150-200 mg/hr IV) may be more effective, because the half-life of 2-PAM is relatively short.

D. GUT & SKIN DECONTAMINATION

- **Lavage v Ipecac.** Ipecac should not be used, because of the potential for abrupt onset of seizures or respiratory arrest. Perform lavage as soon as possible. Protect the airway with an ET tube if the person is obtunded or otherwise compromised.

- **Activated charcoal.** Administer 50-60 gm along with a cathartic (eg, sorbital 70-100 mL). Some studies suggest that chlorinated HCs such as Kepone and Lindane may be eliminated from the body more rapidly with repeated-dose activated charcoal.

- **Skin decontamination.** See prehospital notes above. Even if scene decontamination has been performed, a repeated soap/shampoo wash is recommended for oily or adherent products, along with scrubbing under the nails and in skinfolds.

E. **DIFFERENTIAL DIAGNOSIS.** Consider other intoxications and medical conditions that may present with altered mental status, seizures, and sweating, such as:

- Heatstroke
- Idiopathic seizure disorder
- Salicylate intoxication
- Anxiety/hyperventilation
- CNS infection
- CNS trauma

III. POISON CONTROL CENTER CONSULTATION

San Francisco:	(800) 523-2222
Sacramento:	(800) 342-9293
San Jose:	(800) 662-9886
Fresno:	(800) 346-5922
Los Angeles:	(800) 777-6476
Irvine:	(800) 544-4404
San Diego:	(800) 876-4766

A. **MEDICAL TOXICOLOGY CONSULTATION.** PCCs provide a variety of consultation to calling health professionals and the public, including:

- **Differential diagnosis**

- **Selection of appropriate laboratory tests.** Use of cholinesterase levels; selection of other labs.
- **Use & precautions with antidotes.** Dosage, side-effects, precautions, and other drug information.
- **Medical toxicologist back-up.** Each PCC has a physician toxicologist available 24 hours a day for medical consultation, if needed.

B. **REPORTING REQUIREMENTS.** PCCs can inform callers about State law related to reporting of pesticide illness, and could serve as a 24-hour reporting point for health professionals.

- **Information on reporting rules & forms.**
- **Telephone numbers of local health departments.**
- **Future: official reporting site?** This would increase the likelihood that serious cases are promptly reported. In addition, it would encourage the use of PCC medical consultation and thereby enhance patient care.

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MASTER INDEX OF
HEALTH AND SAFETY (HS) BRANCH REPORTS
LISTED IN NUMERICAL AND (PRIMARILY) CHRONOLOGICAL ORDER

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(This index includes reports up through HS-1629)

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2) HS-949 is an "Alphabetical Index of Health and Safety (HS) Branch Reports by Specific Pesticide".

3) HS-950 is an "Index of Health and Safety (HS) Branch Reports on Occupational Exposure in California Classified by Annual Summary or by Job Category".

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March 6, 1990

Epidemiology of Food Safety

Foodborne Infectious Illness and Contamination with Natural Products

Infections continues to be the leading cause of acute illness associated with food. Among reportable diseases, salmonellosis appears to be the greatest concern, with more than 40,000 cases confirmed annually by isolates of one or more species, exclusive of S. typhi, from stool cultures in U.S., with some increase in the last 10 years. These confirmed cases represent probably a much larger number of unreported cases, in addition to cases of staphylococcal and viral gastroenteritis that are not routinely reported through the Public Health Surveillance System operated by CDC and the state health departments. Notable recent outbreaks have included Listeriosis associated with Mexican-style "Quebracho" cheese and other soft cheeses and an outbreak of salmonellosis associated with pasteurized milk that involved >16,000 culture confirmed cases. The total number of symptomatic cases was estimated to be as high as 300,000.

Contamination of food with natural products has also been a recent issue, illustrated by the occurrence of thyrotoxicosis in the Northern Midwest associated with the ingestion of "extra lean ground beef" containing high levels of T3, T4, and histologically demonstrable chunks of bovine thyroid tissue.

History of Chemical Food Safety Issues

Federal Regulation in U.S. dates back to Pure Food and Drug Act and Meat Inspection Act of 1906, which followed on the heels of publication of **The Jungle** by Upton Sinclair. In addition to foodborne bacterial illness, there was concern about adulteration of food with chemical substances. Synthetic pesticides now in use were unknown, but there were many problems with residues of arsenic on produce that resulted in dramatic episodes of consumer poisoning and consequent promotion of alternative natural insecticides such as derris root.

Since the introduction of synthetic pesticides there have been numerous outbreaks of accidental contamination of food with common insecticides such as parathion, endrin, and toxaphene. Epidemics of acute intoxication continues to be an issue, as illustrated by the 1985 outbreaks of poisoning secondary to aldicarb contaminated watermelons. Recent episodes have included seizures associated with endrin contaminated taquitos and methamidophos (Monitor®) contaminated peppers and cucumbers.

Produce Monitoring Program

Extensive monitoring of produce for pesticide takes place in California, with more than 15,000 samples taken annually by the Department of Food and Agriculture and a few additional samples taken by the US FDA. 8,500 (57%) are taken are taken in the market place surveillance, with 2,500 (17%) taken as preharvest samples and an equal number taken for targeted priority pesticides, and 1,500 (10%) samples taken of produce destined to be used in processed foods. Of all samples taken, 70-90% show

no detected residue, and less than 1% show illegal residues, most commonly low levels of contamination with a material for which no tolerance exists on the crop in question. Rarely, sufficient levels of an acute toxin are detected to warrant a product recall.

Concern About Carcinogenic Effects of Low Level Residues

Potential human carcinogens are usually identified from high dose animal bioassays, conducted at the maximum tolerated dose (MTD) that causes no acute mortality. Concern about the human risk from high dose animal carcinogens depends on one's interpretation of the threshold/non-threshold question in the natural history of cancer. Despite a great deal of research no consensus on this issue has been reached. There is little evidence for an "all-or-none" threshold response, but for some chemicals there is some evidence that the dose-carcinogenic response curve may be non-linear. Recent examples of public concern have been ethylene dibromide and daminozide (Alar®). Given low levels of pesticide residue in produce, there is probably minimal risk in context of overall diet. Dietary concerns that may be of greater concern include total caloric intake and total dietary fat. Concern about carcinogenic effects of pesticides should focus on the workplace. Available data shows there is no increased risk of cancer in the overall California farm workforce. Nevertheless, experience with manufacturing workers exposed to particular products, such as the bladder carcinogen chlordimeform, suggest the need for filling in existing data gaps and minimizing exposure to and/or limiting the use of potent animal carcinogens.

The Western Journal of Medicine

Articles

Subacute Poisoning With Phosalone, an Organophosphate Insecticide

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An illness characterized by weakness, dizziness, and gastrointestinal symptoms was identified among a crew of 30 migrant field-workers employed by a grape grower in Madera County, California, during August 1987. The onset of symptoms occurred between August 24 and August 30 and a median of 9 days from the date of first employment. The first crew member sought medical treatment on August 26, and 10 crew members were admitted to hospital between August 27 and August 30. For most workers, gastrointestinal and constitutional symptoms resolved shortly after admission, but 4 patients had episodes of severe sinus bradycardia persisting for several days. On the day of admission, transient atrioventricular dissociation developed in 2 persons. Interviews with 16 crew members not admitted to the hospital identified only 1 additional worker ill with gastrointestinal symptoms, but all 16 had moderate to severe inhibition of both plasma and red blood cell cholinesterase. Four other workers who were tested but not interviewed also had cholinesterase depression. The crew had had exposure since August 19 to the organophosphate insecticide phosalone, which was last applied to the vineyard on July 21, or 29 days earlier. Although this is the first report unequivocally linking phosalone to field-worker poisoning, the delayed onset and nonspecific nature of the symptoms associated with subacute poisoning may have hindered the recognition of previous similar episodes.

(O'Malley MA, McCurdy SA: Subacute poisoning with phosalone, an organophosphate insecticide. West J Med 1990 Dec; 153:619-624)

Organophosphate pesticides are widely used in modern agriculture. In 1987 the California Department of Food and Agriculture (CDFA) reported more than 15 million lb was sold throughout California.[1] These compounds inhibit acetylcholinesterase, leading to overactivity of portions of the central nervous system dependent on acetylcholine-mediated neurotransmission. In humans with exposure to toxic amounts of organophosphate pesticides, symptoms of acute poisoning commonly include salivation, lacrimation, urination, diarrhea, vomiting, bradycardia, and peripheral weakness or paralysis.[2] When poisoning is severe, central nervous system effects such as seizures and coma may also occur and may culminate in death. Symptoms of organophosphate toxicity are nonspecific, and the diagnosis requires a high degree of clinical suspicion.

In recent years outbreaks of organophosphate poisoning in California field-workers have frequently involved large groups presenting to the emergency department of a rural hospital for evaluation of acute gastrointestinal symptoms after a single accidental overexposure to a highly toxic organophosphate insecticide.[3] In this context, group and individual cholinesterase data may be difficult to interpret, but the common exposure history and epidemic nature of the illness facilitate diagnosis.[4] In cases of accidental or deliberate ingestion of organophosphates, diagnosis is facilitated by the recent history of ingestion. There is typically an interval of less than 24 hours between the exposure and the start of symptoms.[5]

Individual cases of field-worker poisoning may prove difficult to identify without a recognized outbreak of illness. As illustrated by the series we report here, recognition may be especially difficult when the gradual absorption of a moderately toxic organophosphate leads to a subacute onset of symptoms. Although fully apparent illness may eventually develop in a small number of cases, some persons may be asymptomatic or may have mild and nonspecific symptoms despite marked cholinesterase inhibition. The clinical syndrome of subacute intoxication shown by the most severely affected patients may differ from that seen in acute poisonings, as illustrated in our series by the occurrence of atrioventricular dissociation and severe bradycardia without excess respiratory and gastrointestinal tract secretions typical of acute cholinergic crisis.

Patients and Methods

California law requires physicians to report confirmed and suspected cases of pesticide poisoning to the appropriate county health officer. These reports are then forwarded to the county agricultural commissioner's office for investigation of the circumstances of pesticide exposure. Authorities in the California Department of Health Services and the CDFA are also notified. Work-related cases may also enter into the reporting network on a physician's filing of a Workers' Compensation report with the state Department of Industrial Relations.[6]

Our series involves an incident of poisoning by the insecticide phosalone (S-[(6-chloro-2-oxo-3[2H]-benzoxazolyl) methyl] O,O-diethylphorodithioate) that was reported to the CDFA during August (and September) of 1987. The investigation of these cases involved interviewing affected and unaffected employees by officials from the state and county agricultural departments; reviewing grower application histories; sampling implicated fields for pesticide residues; and examining in detail medical records for all exposed persons who sought medical treatment.

The suppression of cholinesterase activity was quantita-

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ABBREVIATIONS USED IN TEXT

CDFA = California Department of Food and Agriculture
LD_{50} = minimum lethal dose

tively estimated from the midpoint of the normal range, using the method of Namba and co-workers.[5] The relationship between cholinesterase depression and several postulated exposure factors was evaluated using the Wilcoxon rank sum test for independent samples.[7] Factors evaluated included work history, sources of food, place of residence, the use of irrigation water for washing clothes or bathing, and the presence of symptoms. Information on work history and sources of food and water was obtained exclusively from interviews. Where a direct interview was not possible, addresses and information regarding the presence or absence of symptoms were obtained from medical records. All chemical residue measurements were carried out by Chemical Laboratory Services at CDFA, including dislodgeable foliar residue samples for phosalone and multiresidue screens for carbamates and other organophosphates.

Results

Report of Cases

On August 26, 1987, a 25-year-old man (patient 1) sought treatment at a community hospital in Madera County, California, because of dizziness, disorientation, and vomiting that began while he was harvesting grapes for a Madera grower (grower A) that afternoon. No other members of the 30-man crew were ill. His pulse rate and other vital signs were normal; the findings of a physical examination were unremarkable except for mild epigastric and suprapubic tenderness. A complete blood count and chemistry panel—serum creatinine, potassium, sodium, carbon dioxide, chloride, calcium, and glucose levels—were within normal limits. A diagnosis of acute gastroenteritis was made. After receiving 2.5 liters of 5% dextrose in a solution of 0.25 normal saline, the patient felt better and was discharged.

He returned at 12:40 PM the next day because of persistent weakness and dizziness associated with the occurrence of diarrhea, crampy abdominal pain, lacrimation, and salivation. On reexamination, he appeared weak and his pulse rate was 48 beats per minute; his blood pressure and respiratory rate were normal. His pupils were 3 mm in diameter, the lungs were clear, and the abdomen was nontender. Laboratory examinations again showed a normal complete blood count, chemistry panel, and urinalysis. The plasma cholinesterase level was 304 units per liter (normal, 904 to 2,400); the erythrocyte cholinesterase content was 4,360 units per liter (normal, 9,348 to 16,996). At 2:35 PM he had an episode of severe bradycardia with a supraventricular rhythm of 32 beats per minute (Figure 1, top). His blood pressure was 109/74 mm of mercury, but there was no notation describing symptoms or postural changes in the blood pressure. He received 1 mg of intravenous atropine, and in several minutes his heart rate increased to 60 beats per minute.

On admission to the hospital, the patient was given a second dose of 1 mg of atropine intravenously and was placed on cardiac telemetry. Because of recurrent episodes of moderate bradycardia, he required a total of 4.5 mg of atropine on his first hospital day (Table 1). Severe bradycardia recurred at 5:00 AM on the second hospital day (heart rate, 37 beats per minute) and again at 7:34 AM, with an initial sinus pause of 2.6 seconds, followed by recovery to an estimated heart rate of 39 beats per minute (Figure 1, bottom). After a dose of atropine, his heart rate increased to 75 beats per minute. During the next several days, the patient received frequent doses of atropine for episodes of moderate sinus bradycardia. Except for an intermittent headache, nausea, and a single episode of loose stool reported on the seventh hospital day, he was asymptomatic and his lungs remained clear to auscultation. He was asymptomatic on discharge but had persistent mild bradycardia. A total of 16.5 mg of atropine was administered throughout his eight-day hospital stay (Table 1).

Although other crew members were asymptomatic when patient 1 first reported symptoms, on August 29, a 15-year-old boy (patient 2) collapsed at the same labor camp shortly after work. He was taken by an acquaintance to the community hospital along with two other members of the crew (patients 3 and 4). All three had nausea and abdominal cramping and were later admitted. Cholinesterase values were well below the lower limit of normal (Table 1). On instructions from the emergency department staff, the acquaintance returned to the labor camp to see if any additional camp residents were ill. As a result, patients 5 through 10 were admitted to the hospital late in the evening of August 29 or early in the morning of August 30 with symptoms as shown in Table 1.

Patients 3, 5, and 6 each had severe bradycardia comparable to that of the index case. Aside from postural dizziness suffered by patient 5 on the third hospital day, none were symptomatic when these episodes occurred. Patient 6 also had episodes of atrioventricular dissociation at 6:34 AM and 5:43 PM on the first day in the hospital (Figure 2, top and bottom). Hospital records showed that the workers were asymptomatic when discharged (between September 3 and September 5), but many still had a mild sinus bradycardia (between 50 and 60 beats per minute).

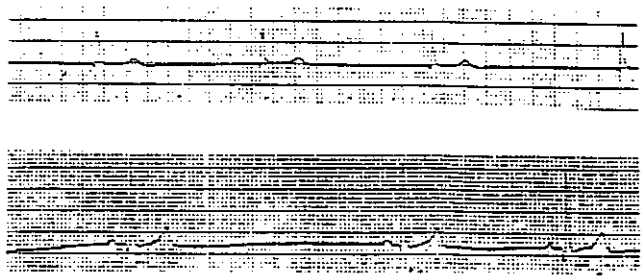

Figure 1.—Cardiac telemetry strips taken on patient 1 show episodes of severe bradycardia: **Top**, On first hospital day at 2:35 PM, patient had a supraventricular rhythm of 32 beats per minute. **Bottom**, On second hospital day at 7:34 AM, there was a 2.6-s sinus pause followed by recovery to about 39 beats per minute.

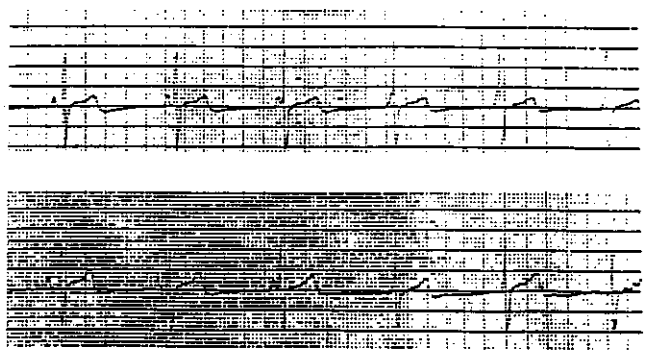

Figure 2.—Cardiac telemetry strips taken on patient 6 on first hospital day show episodes of atrioventricular dissociation at (top) 6:46 AM and (bottom) 5:43 PM.

TABLE 1.—*Summary of Clinical Course of 10 Patients Admitted to Hospital With Subacute Phosalone Poisoning*

Patient	Age, yr	Date	Symptoms	Cholinesterase Level,* U/liter		Lowest Heart Rate, bpm	Atropine, mg	Pralidoxime, grams	Telemetry Findings
				Plasma	RBC				
1	25	8/27	Vomiting, diarrhea, dizziness, disorientation, lacrimation, salivation, abdominal cramps	304	4,360	32	4.5	None	SB
		8/28	Headache, nausea	362	4,680	30	5.0	...	SB
		8/29	None	545	5,080	44	2.0	...	SB
		8/30	Headache	609	6,200	40	1.0	...	SB
		8/31	None	724	5,280	46	3.0	...	SB
		9/1	Headache, nausea	864	5,720	46	1.0	...	SB
		9/2	Loose stool, abdominal cramps	1,084	6,020	50 to 60	...	...	SB
		9/3	Discharged	...	...	...	...	...	
2	15	8/29	Dizziness, nausea, abdominal cramps, vomiting	326	4,920	68	...	None	None
		8/30	None	...	...	72	...	...	
		8/31	Discharged	...	...	48	...	...	
3	24	8/29	Dizziness, nausea, abdominal cramps, vomiting	244	3,200	56	0.6	...	SB
		8/30	None	...	...	45	...	1	SB
		8/31	None	454	4,800	43	...	1	SB
		9/1	None	560	4,120	37	0.5	1	SB
		9/2	Discharged	...	...	44	...	...	SB
4	23	8/29	Weakness, nausea, abdominal pain, dizziness	346	4,680	60	None	None	None
		8/30	None	...	...	72	...	...	
		8/31	Headache	...	...	54	...	...	
5	44	8/30	Weakness, dizziness	260	3,760	38	4.0	1	SB
		8/31	None	394	5,400	42	0.5	...	SB
		9/1	Dizziness on rising	557	6,440	36 to 38	2.0	...	SB
		9/2	None	810	7,800	39	1.5	...	SB
		9/3	None	782	6,320	39	0.5	...	SB
		9/4	None	864	7,440	48	...	...	SB
		9/5	Discharged	...	...	...	...	...	None
6	19	8/30	Weakness	501	5,160	39	3.5	1	SB, AV dissociation
		8/31	None	644	6,760	38	2.5	...	SB
		9/1	None	821	7,240	34	1.0	...	SB
		9/2	None	968	8,040	53	...	...	SB
		9/3	None	924	7,240	34	1.5	...	SB
		9/4	Chest pain, headache	951	12,800	52	...	...	SB
		9/5	Discharged	...	...	...	...	...	
7	69	8/30	Weakness	238	3,880	50 to 55	0.5	1	SB
		8/30	None	303	6,160	...	...	...	
		8/31	None	385	6,080	48	...	...	SB
		9/1	None	582	6,200	72	...	...	None
		9/2	None	760	7,960	52	...	...	None
		9/3	None	834	8,280	NR	...	...	None
8	54	8/29	Nausea, headache, abdominal pain, dizziness	270	4,000	60	...	1	SB
		8/30	None	346	4,240	58	...	...	SB
		8/31	Headache	435	7,000	61	...	...	SB
		9/1	None	664	8,280	46	1.0	...	SB
		9/2	None	805	6,820	50	...	...	
		9/3	None	793	6,760	54	...	...	
9	18	8/29	Nausea, vomiting, dizziness, abdominal tenderness	330	4,920	60	...	None	None
		8/30	None reported	360	5,520	58	...	1	SB
		8/31	None reported	474	7,560	53	...	...	SB
		9/1	None reported	678	8,360	52	...	...	SB
		9/2	None reported	844	7,800	...	...	...	None
		9/3	Discharged	...	...	...	...	...	
10	49	8/29	Dizziness, salivation, headache	320	3,680	56	None	1	SB
		8/30	None reported	382	4,480	56	...	...	SB
		8/31	None reported	537	9,400	60	...	...	SR
		9/1	None reported	737	8,400	64	...	...	None
		9/2	None reported	960	6,360	>50	...	...	
		9/3	Discharged	930	11,040	...	...	...	

AV = atrioventricular, NR = not recorded, RBC = erythrocyte, SB = sinus bradycardia, SR = sinus rhythm

*Cholinesterase tests done using modified Ellman (colorimetric) method. Normal range: RBC cholinesterase, 9,348 to 16,996 (midpoint is 13,172); plasma cholinesterase, 964 to 2,400 (midpoint is 1,682).

Except for bradycardia, there were few signs of cholinergic crisis among the 10 patients during their hospital stays. Although patient 3 had chest tightness on admission, he never showed respiratory distress, and his lungs remained clear to auscultation.

On August 31 and September 1, the remaining members of the harvesting crew had cholinesterase tests, and all but four were available for interview on September 2. These interviews revealed an unreported case of gastrointestinal symptoms in a crew member (patient 27) whose date of symptom occurrence corresponded to the dates reported by the 10 patients previously admitted to the hospital (Figure 3). Crew member 28 reported atypical symptoms that did not begin until September 6; this member was counted as asymptomatic in the subsequent analysis.

Results of the cholinesterase tests showed that all crew members had enzyme activity levels depressed far below the predicted values (Table 2). For the crew as a whole, the median degree of plasma cholinesterase inhibition was 64.9%; for erythrocyte cholinesterase, the median degree of inhibition was 52.5%. The degree of cholinesterase inhibition was not influenced by previous work done during the 1987 harvest season or by the consumption of grapes at home or at work (Table 3). It was noted that the 11 symptomatic workers had a significantly greater degree of cholinesterase inhibition than did the 15 who were asymptomatic (Figure 4). Although the use of the irrigation canal for washing clothes or bathing was suspected as a possible source of exposure, it proved to have a significant negative relationship with the occurrence of cholinesterase depression. Crew members who did not live at the camp may have

TABLE 2.—*Cholinesterase Values for Crew Members With Subacute Phosalone Poisoning Not Admitted to Hospital**

	Plasma Cholinesterase		RBC Cholinesterase		
Crew Member	Measured Value	% Below Midpoint of Normal Range	Measured Value	% Below Midpoint of Normal Range	Symptoms
11	788	53.2	4,800	63.6	None
12	690	59.0	7,680	41.7	†
13	608	63.9	6,760	48.7	None
14	809	51.9	6,440	51.1	None
15	695	58.7	6,520	50.5	†
16	638	62.1	6,520	50.5	None
17	749	55.5	7,000	46.9	None
18	562	66.6	6,520	50.5	None
19	573	65.9	8,600	34.7	None
20	1,167	30.6	6,440	51.1	†
21	1,035	38.5	6,520	50.5	†
22	868	48.4	5,160	60.8	None
23	674	59.9	6,080	53.8	None
24	1,108	34.1	8,360	36.5	None
25	769	54.3	6,760	48.7	None
26	939	44.2	6,640	49.6	None
27	0.26	74.8	0.37	58.9	Indigestion, stomach pains, vomiting, nausea, tingling of body
28	0.18	82.5	0.26	71.1	Numbness in tongue
29	0.31	69.9	0.49	45.6	None
30	0.20	80.6	0.40	55.6	None

RBC = erythrocyte

*Cholinesterase tests for crew members 27 through 30 were done using the Michel method at a referral laboratory in Fresno, California. Normal range in δ pH units: RBC cholinesterase, 0.55 to 1.25 (midpoint is 0.90); plasma cholinesterase, 0.41 to 1.65 (midpoint is 1.03). Other tests were carried out using the Ellman method at the hospital laboratory. Normal range in units per liter: RBC cholinesterase, 9,348 to 16,996 (midpoint is 13,172); plasma cholinesterase, 964 to 2,400 (midpoint is 1,682).

†Crew member was not available for interview.

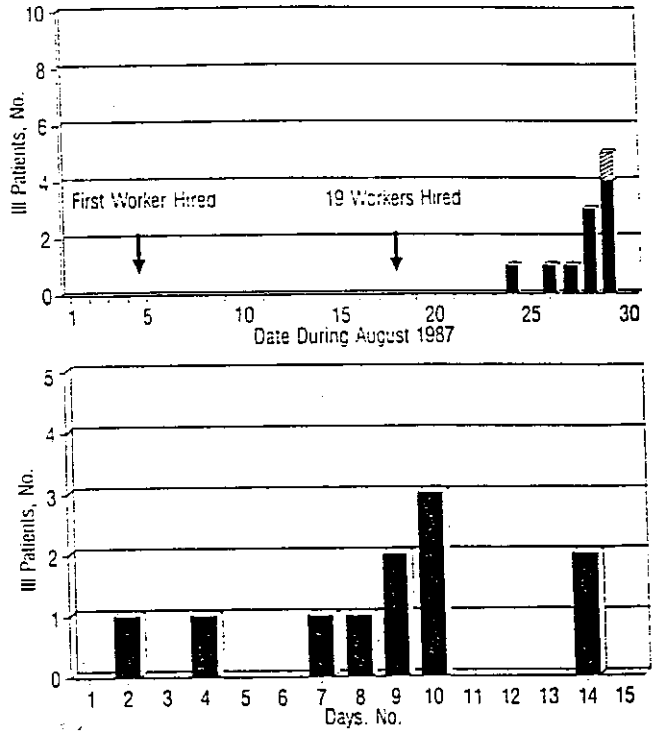

Figure 3.—The graphs show the distribution of cases by time of occurrence: Top, Cases are shown by date of onset; bottom, cases are shown by latency between first exposure and start of symptoms. ■ = patient admitted to hospital, ▨ = patient not admitted

TABLE 3.—*Investigation of Factors Postulated to Affect Cholinesterase Depression*

Factor	Number Exposed	Estimated % Inhibition Median Value		Number Unexposed	Estimated % Inhibition Median Value			
		RBC	Plasma		RBC	P Value*	Plasma	P Value*
Labor camp residence	19	61	70	7	51	.236	61	.112
Prior work, Mexico	8	52	68	16	60	.540	72	.760
Prior work, Oregon	10	56	64	14	57	.770	78	.219
Bathing or washing in irrigation canal	12	49	63	10	69	.001	81	.003
Ate grapes at work	16	57	72	8	59	.783	64	.951
Ate grapes at home	6	50	67	18	62	.155	72	.640
Food provided by crew supervisor	13	67	80	6	57	.254	77	.930
Symptomatic illness	11	68	81	15	51	.002	60	.001

RBC = erythrocyte

*Based on the difference between exposed and unexposed groups in the Wilcoxon rank sum test.

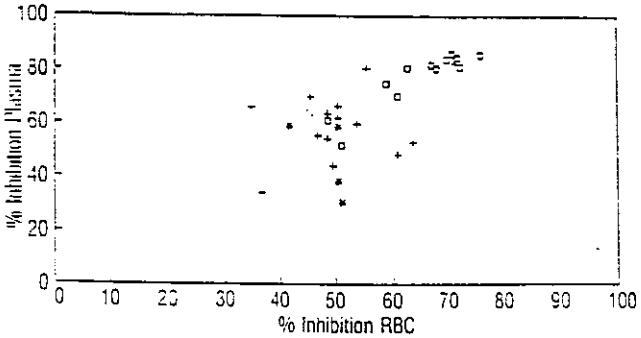

Figure 4.—The percentage of depression for plasma and erythrocyte (RBC) cholinesterase levels is shown in symptomatic and asymptomatic workers. □ = worker with gastroenteritis, + = asymptomatic worker, • = worker not interviewed

had even less adequate facilities. Five crew members (14, 18, 22, 24, and 30) reported that they slept either in their automobiles or in the fields since they began working for the Madera County grape grower and had no temporary residence during their stay in Madera.

Work History and Pesticide Residue Data

On investigation of these illnesses by the Madera County Agricultural Commissioner's Office, it was found that before mid-August, crew members had no common exposure history. Several persons reported having worked previously in Oregon, others in Idaho, and still others in southern Santa Clara County and the San Joaquin Valley of California. Dates of employment in Madera County ranged from August 5 to August 26, but most crew members began work for grower A on August 19, manually harvesting a block of French Colombard grapes. This block had been treated May 15 with 25% phosalone wettable powder (7 lb per acre). On July 21 various rows in this block received a second application of phosalone emulsifiable concentrate at 5 pt per acre and phosalone wettable powder at 3 lb per acre. The seven-day interval to allow safe reentry into phosalone-treated fields[8] elapsed on July 28, one week before the first worker entered the field (Figure 3).

Other blocks worked between August 19 and August 26 included 35 rows of Thompson seedless grapes treated with 25% phosalone wettable powder at 7 lb per acre on May 15. According to the grower's application records, all blocks within the vineyard had received at least one treatment with phosalone, during either May or July, and no other cholinesterase-inhibiting insecticides were applied during the 1987 growing season. This was confirmed by chemical analysis of field samples showing persistence of phosalone (13 dislodgeable foliar residue samples with levels ranging from 0.3 to 2.0 μg per cm^2; median value, 1.3 μg per cm^2) and its toxic transformation product, phosalone-oxon (ranging from nondetectable to 0.29 μg per cm^2; median value, 0.12 μg per cm^2). All samples were thus below the 7.0 μg per cm^2 dislodgeable foliar residue estimated as a safe level for preventing cholinesterase inhibition and acute poisoning in field-workers.[9] In none of the 13 samples taken was residue of any other cholinesterase-inhibiting insecticide found.

Discussion

This series of poisonings associated with the insecticide phosalone underlines the unpredictable relationship between cholinesterase inhibition and the occurrence of related symptoms. Although there was a significant statistical relationship between symptoms and cholinesterase depression in the crew as a whole, some workers with greater than 80% depression of plasma cholinesterase levels remained asymptomatic. The absence of symptoms in most crew members is likewise unexpected when cholinesterase data from the current outbreak are compared with previous case series involving the acute onset of organophosphate poisoning.[3-5] This finding strongly suggests that both the rate and the magnitude of cholinesterase depression are important determinants of symptomatic illness after exposure to organophosphate insecticides.

The principal clinical features of interest in this series were the atrioventricular dissociation and severe sinus bradycardia among the patients admitted to the hospital. Atrioventricular dissociation and bradycardia were unexpected because cardiac side effects of organophosphate exposure have usually been associated with an acute overdose of the agent, accompanied by florid signs of cholinergic overstimulation.[10-12] Although the bradycardia was well tolerated during bed rest or relative inactivity, six of the ten patients receiving hospital care initially presented with symptoms of dizziness or syncope, and one patient (patient 5) had transient postural dizziness on his third day in the hospital. These symptoms may have been due to direct pharmacologic effects of acetylcholine on the central nervous system, but they could also plausibly be explained by the severe bradycardia shown by four of the eight patients monitored with cardiac telemetry. Because few cases of acute phosalone intoxication have previously been published, it is impossible to ascertain whether the prominent cardiac effects seen in these persons were attributable primarily to the slow onset of poisoning or were a unique feature of illness after exposure to phosalone.

The outbreak reported here is the first instance in which phosalone has been identified as the principal agent responsible for a mass field-worker poisoning incident. Although it has previously been implicated in conjunction with other organophosphate pesticides, phosalone's moderate toxicity (for rats, minimum oral lethal dose [LD_{50}] is 120 mg per kg and the dermal LD_{50} is 1,530 mg per kg[13]) made it seem a less likely cause of those outbreaks than were other, more toxic compounds.[14-16] The finding of dislodgeable residue levels below the estimated safe level[9] of 7.0 μg per cm^2 also militated against phosalone's being a contributing cause in each of the previous episodes. An investigation of the episode reported here, however, shows that illness may occur at residue levels well below 7.0 μg per cm^2. After the investigation of this outbreak, two similar phosalone-related outbreaks of illness—also accompanied by cases of asymptomatic cholinesterase depression—were reported at the beginning of September 1987.[17] Emergency restrictions on harvesting phosalone-treated vineyards were then imposed for the remainder of the harvest season (September, October, and November of 1987).

A principal distinction between phosalone and other organophosphate insecticides is its environmental persistence. General surveys of hand-harvest operations in California, involving samples collected by CDFA between 1975 and 1984, have shown that harvester exposure to organophosphate residues is intermittent, with only 6% of the 2,088 fields sampled in this series having detectable residue levels.[18] Phosalone, by contrast, typically persists well beyond its seven-day reentry period; and in California's Central Valley, its environmental half-life ranges as long as 30 days.[19-23] Given the recognition of illness in field-workers associated with phosalone levels of 0.3 to 2.9 μg per cm^2 dislodgeable foliar residue (following applications made more than a month earlier), adjustment of the reentry inter-

val was deemed an impractical method of regulating this compound, except for use on machine-harvested crops. By agreement between CDFA and the manufacturer, phosalone use in California was therefore eliminated for all manually harvested crops beginning in 1988.

Conclusion

To treating physicians, a physiologic adaptation to cholinesterase inhibition seen in subacute organophosphate poisoning presents many clinical dilemmas. Should patients presenting with only mild sinus bradycardia be admitted to the hospital, and should all these patients be monitored routinely with cardiac telemetry? Does moderate to severe bradycardia with no other symptoms of cholinesterase inhibition warrant the aggressive use of atropine recommended for serious acute poisonings?[24] Should the use of pralidoxime be recommended despite the expectation of only a partial recovery of cholinesterase activity? Although it is evident that a careful observation of patients for episodes of severe bradycardia is warranted, the other questions cannot be answered with certainty and deserve careful consideration in each case of organophosphate poisoning.

Clinicians must recognize that some incidents of poisoning among agricultural workers may represent "sentinel health events."[25] As we have shown here, it is appropriate to seek an evaluation of co-workers when it has been determined that one field-worker or a small group has been poisoned. Given a lengthy and variable delay between the exposure and the occurrence of symptoms, persons with subacute poisoning are more likely to present for medical evaluation singly or in small groups. Many patients with no or mild symptoms may therefore escape medical attention. Although less likely to present as illness clusters, pesticide applicators who handle organophosphates may also be at risk for subacute poisoning. Physicians' awareness of the spectrum of pesticide illness among field-workers is essential for the recognition, treatment, and prevention of poisoning with cholinesterase-inhibiting insecticides.

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Acetylcholinesterase Assays: What Do They Mean? How To Use Them.

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I. Inhibition of Red Blood Cell Acetylcholinesterase and Serum Non-Specific Cholinesterases Indicate Exposure to Organophosphate and Organocarbamate Esters.

A. Cholinesterases hydrolyze esters of choline in a multi-step enzyme reaction.

B. Organophosphate esters and carabamate esters bind to cholinesterases, but are not rapidly released, inhibiting the enzymes.

1. Carbamates are readily hydrolyzed from cholinesterases. Diluting the blood before assaying promotes reactivation.

2. Organophosphates bind more firmly than carbamates, especially when a group leaves the phosphate and "aging" occurs.

II. Agricultural Workers In California Using Categories I and II Pesticides Are Required To Have Blood Cholinesterase Tests.

A. Baseline tests are taken, preferably when the workers have not been exposed to pesticides for 30 days.

B. Employees working with Category I chemicals are tested more often than others.

C. A drop to 80% of baseline signals retesting.

D. Decrease to 70% of RBC AChE level or to 60% of plasma cholinesterase indicates the worker should be removed from the workplace.

III. Laboratories Determining Blood Cholinesterases Are Approved By The California Department Of Health Services (CDHS).

IV. Normal Tables Should Be Consulted For Patients Without Baseline Values.

A. Each laboratory is expected to provide values for the assay they use.

V. Kinds Of Assays Approved By CDHS.

A. Assays using acetylcholine and pH changes
   1. Michel Test
   2. pH Stat

B. Assays using acetylthiocholine and colorimetry
   1. Reaction rate determinations
   2. End point automated assays

VI. Preparation of Blood For Assaying.

A. Check with the laboratory first

B. Use heparin to prevent clotting.

C. Separating red blood cells and plasma is preferable if they are to be assayed individually.

VII. New Techniques.

A. Antibodies

B. Oxime reactivation

Acetylcholinesterase Assays: What Do They Mean? How To Use Them.

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UNCOMMON ASSASSINS:
POISONING BY SELECTED UNCOMMON OR UNUSUAL PESTICIDES

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VARIETY OF PESTICIDES USED FOR VARIETY OF PURPOSES

- Insecticides
  - Organophosphates
  - Carbamates
  - Organochlorines
- Herbicides
  - Bipyridyls
  - Chlorophenoxy compounds
- Fungicides
  - Captan
  - Pentachlorophenol
- Fumigants
  - Hydrogen cyanide
  - Methyl bromide
  - Phosphine
  - Sulfuryl fluoride

ORGANOCHLORINES

INTRODUCTION

* Widely used in agriculture & structural pest control
* Lindane also used for treatment of lice and scabies
* Many products now banned because they persist in the environment and accumulate in biologic systems
* Have been largely replaced by organophosphates

PHARMACOLOGY / MECHANISM OF TOXICITY

* Well-absorbed from GI tract, skin, and by inhalation
* Highly lipid soluble (large volumes of distribution)
* Accumulate with repeated exposure, very slow elimination
  Example: accumulated DDT eliminated at a rate of approx only 1% per day, with a half-life of 6-12 months.
* Interfere with transmission of nerve impulses, especially in the brain - potent CNS toxins
* May sensitize myocardium to arrhythmogenic effects of catecholamines
* Many can cause liver and/or renal injury

TOXIC DOSE

* Acute toxic dose highly variable
* Extensive or repeated whole-body application of lindane to infants has resulted in seizures and death

Compound	LD50 in Male Rats ORAL	DERMAL	Approx Lethal Human Dose
Aldrin	39 mg/kg	98 mg/kg	3-7 gm
Chlordane	335	840	2-6
Dieldrin	46	90	2-5
DDT	217	2,510	-
Endrin	18	18	-
Heptachlor	100	195	-
Lindane	88	1,000	10-30
Mirex	740	>2,000	-

CLINICAL PRESENTATION

* Nausea and vomiting shortly after exposure
* Confusion, tremor, seizures
* Coma and respiratory depression
* Arrhythmias may occur due to catecholamine sensitivity
* Because of high lipid solubility, toxicity may be prolonged
* Signs of hepatitis or renal injury may develop

DIAGNOSIS

* Based upon history of exposure and clinical presentation
* Blood levels generally not available

GENERAL TREATMENT

* Control seizures & protect airway, assist ventilation
* Monitor asymptomatic patient for at least 6-8 hours
* Ventricular arrhythmias may respond to propranolol
* No specific antidotes

DECONTAMINATION

SKIN:

* Highly contaminating - rescuers should wear proective gear
* Remove clothing, wash skin & hair with copious soap/water
* Irrigate exposed eyes with copious tepid water or saline

INGESTION:

* Do NOT induce emesis because of risk of seizures
* Perform gastric lavage and administer activated charcoal

ENHANCED ELIMINATION:

* Repeated doses of activated charcoal or cholestyramine?
* No benefit with hemodialysis or hemoperfusion

PENTACHLOROPHENOL

INTRODUCTION

* Chlorinated aromatic hydrocarbon
* Herbicide, fungicide, wood preservative and defoliant

PHARMACOLOGY / MECHANISM OF TOXICITY

* Readily absorbed through skin, lungs and GI tract
* Most accidental poisonings involve skin absorption
* Elimination half-life 30-80 hours
* Uncouples oxidative phosphorylation in mitochondria, resulting in generalized increase in metabolic activity
* Fetotoxic in rats when given in the first trimester

TOXIC DOSE

* Minimum human lethal dose not known, but serious intoxication reported after ingestion of 2 gm
* Air level considered immediately dangerous to life or health (IDLH) is 150 mg/m3
* OSHA permissible exposure limit (PEL) is 0.5 mg/m3

CLINICAL PRESENTATION

* Irritation of skin, eyes and upper respiratory tract
* Headache, vomiting, weakness, sweating, and dyspnea
* Fever, tachycardia, tachypnea, convulsions and coma
* Death due to cardiovascular collapse &/or hyperthermia
* Pancreatitis, hepatitis, aplastic anemia with chronic exposure

DIAGNOSIS

* Should be suspected in patients with fever, metabolic acidosis, diaphoresis and tachypnea
* Consider also dinitrophenol or salicylate poisoning
* Blood levels not readily available

GENERAL TREATMENT

* Maintain airway and assist breathing if necessary
* Treat seizures with usual anticonvulsants
* Treat hyperthermia with aggressive cooling
* No specific antidote
* Monitor for at least 6 hours after exposure

DECONTAMINATION

SKIN:

* Remove clothing and wash exposed areas with soap and water
* Contaminating - rescuers should wear protective gear

INGESTION:

* Do NOT induce emesis because of risk of seizures
* Perform gastric lavage and administer activated charcoal

ENHANCED ELIMINATION:

* No evidence for efficacy of dialysis or hemoperfusion
* ? Repeated dose activated charcoal

2,4-D & CHLOROPHENOXY HERBICIDES

INTRODUCTION

* Widely used herbicides
* "Agent orange" was a mixture of 2,4-D and 2,4,5-T which also contained small amounts of TCDD (dioxin)

MECHANISM OF TOXICITY

* In plants, act as growth hormone stimulators
* Mechanism of toxicity in animals not known: widespread muscle damage occurs, and cause of death is usually ventricular fibrillation
* Skin not a significant route of absorption

TOXIC DOSE

* Animal oral LD50s 100-1000 mg/kg
* Minimum human toxic dose of 2,4-D is 3-4 gm or 40-50 mg/kg
* Death has occurred after adult ingestion of 6.5 gm

CLINICAL PRESENTATION

* Muscle weakness and muscle spasms, massive rhabdomyolysis
* Tachycardia, severe and intractable hypotension
* Hepatitis and renal injury may occur

DIAGNOSIS

* History of exposure to an herbicide, elevated CPK
* Specific blood levels not routinely available

GENERAL TREATMENT

* Protect airway and assist ventilation if necessary
* Treat rhabdomyolysis with fluids, IV bicarbonate
* No specific antidote
* Monitor patient closely for 6-12 hours after ingestion because of potential for delayed onset toxicity

DECONTAMINATION

* Empty stomach with emesis or gastric lavage
* Administer activated charcoal

ENHANCED ELIMINATION:

* No proven role for dialysis or hemoperfusion
* Alkalinization of urine may promote excretion of 2,4-D

METHYL BROMIDE

INTRODUCTION

* Odorless and colorless gas with poor warning properties
* Liquefies at 3 degrees C
* Fumigant, fire extinguisher, and chemical intermediate

PHARMACOLOGY / MECHANISM OF TOXICITY

* Gas is well-absorbed by inhalation and skin exposure
* Retention of gas in clothing and rubber boots can be a source of prolonged percutaneous exposure
* Mechanisms in include inhibition of sulfhydryl enzymes, methylation of proteins, depletion of cellular glutathione
* NIOSH considers MeBr a potential occupational carcinogen

TOXIC DOSE / AIR LEVEL

* OSHA workplace permissible exposure limit (PEL) is 5 ppm
* Toxic effects common at 200 ppm
* Level immediately dangerous to life or health is 2,000 ppm
* Poor warning properties: significant exposure can occur before onset of symptoms

CLINICAL PRESENTATION

* Irritation of eyes, skin, mucous membranes, and upper respiratory tract
* Pulmonary edema - may be delayed onset
* Skin exposure - dermatitis and chemical burns
* Systemic toxicity - malaise, visual disturbances, headache, nausea, vomiting, vertigo, tremor, seizures, and coma
* Chronic persistent neurological sequelae

DIAGNOSIS

* Based on history of exposure and typical symptoms.
* Serum bromide levels may be elevated but do not correlate with severity of intoxication

GENERAL TREATMENT

* Secure patent airway and assist ventilation if necessary
* Observe for minimum of 6-12 hours after exposure
* No proven specific antidote, although some authors recommend BAL or N-acetylcysteine

DECONTAMINATION:

* Rescuers must wear self-contained breathing apparatus
* Remove from exposure and administer supplemental oxygen
* Remove clothing and wash affected areas with soap and water

ENHANCED ELIMINATION:

* Not effective

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Designated as a Regional Poison Control Center by the American Association of Poison Control Centers

Operated under the auspices of:
Denver Department of Health and Hospitals
University of Colorado Health Science Center
Organized Health Departments of Colorado

United Way
A United Way Agency

SUPERWARFARINS

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I. Introduced as rodenticides because they are effective in warfarin resistant rodents and less is required for effectiveness. LD_{100} of warfarin in mice 0.025% x 21 days.
LD_{100} of brodifacoum in mice is 0.005% x 1 day (Lund, 1981)

II. Mechanism of action.
- A. Block Vit K epoxide reductase which converts Vit K metabolite back to active cofactor.
- B. Superwarfarins more effective because of higher liquid solubility, better liver concentration, binding to epoxide reductase less reversible.

III. Specific agents.
- A. 4 - hydroxycoumarin derivatives.
  1. brodifacoum
  2. difenacoum
  3. bromadiolone
- B. indandione derivatives
  1. chlorophacinone
  2. diphacinone
  3. pindone
  4. valone

IV. Human toxicity
- A. Case reports of sever prolonged anticoagulation in suicidal patients with chronic ingestion. (Barlow, 1982; Chong, 1986; Lipton, 1984; Jones, 1984; Murdoch, 1983)
- B. One case report of a single massive ingestion (200 g) in an adult resulting in severe coagulapathy for 2 months.
- C. Reports of single acute ingestions in children indicate anticoagulation in 7%.
  1. 8/110 cases in children reported to the Rocky Mountain Poison Center August 86 - April 87 had PT ratio $\geq$ 1.2 (Smolinske, 1987).
  2. 48 hour PT was more likely to be abnormal than the 24 hour PT.
  3. Unfortunately, abnormal PT did not correlate with amount ingested by history or dye coloration in child's mouth.

V. Treatment
- A. Prevention
- B. Detection
- C. Supportive
- D. Reversal - Vit K_1, FFP, whole blood.

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PARAQUAT INTOXICATION

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INTRODUCTION

1. 1,1-dimethyl-4,4-bipyridyldiylium ion

2. Quick-acting herbicidal action:
   * contact action on leaves
   * systemic effects

3. Rapidly inactivated in soil

4. Formulated as aqueous solution:
   * 0.2% (domestic uses) up to 21% (agricultural use)

MECHANISM OF TOXICITY

1. Corrosive effects:
   * strong cation in aqueous solution (mainly seen with more concentrated solutions 10-20%)

2. Cellular toxicity:
   * generation of superoxide radicals results in lipid peroxidation and cellular necrosis, depletion of NADPH

PHARMACOKINETICS

1. Relatively poorly absorbed from GI tract & skin:
   * only 5-10% of an oral dose is absorbed
   * food in stomach drastically limits absorption
   * may be absorbed across abraded but not intact skin

2. Widely distributed to tissues:
   * volume of distribution 2.8 L/kg
   * selective accumulation in lung (type II pneumocytes) over several hours; prolonged with renal failure

3. Eliminated unchanged by kidney:
   * 80% eliminated within 24 hours
   * paraquat-induced renal failure delays elimination

TOXIC DOSE

1. Animal oral LD50 varies from 22-262 mg/kg

2. Human toxicity:

* < 5 mg/kg probable mild
* > 30 mg/kg probable lethal (1 gulp of 20% solution)

CLINICAL MANIFESTATIONS

1. Caustic effects:
   * mainly with more concentrated solutions 10-20%
   * skin/eyes: erythema, ulceration
   * oral, esophageal and gastric ulceration
   * vomiting, abdominal pain, diarrhea

2. Multisystem toxicity:
   * myocarditis, cardiogenic shock
   * renal tubular necrosis
   * hepatic failure
   * with dose > 30 mg/kg, death may occur in 1-2 days

3. Delayed pulmonary toxicity:
   * usually seen with doses between 5-30 mg/kg
   * chronic progressive irreversible fibrosis
   * usually fatal after 1-2 weeks

DIAGNOSIS

1. Blood paraquat levels (available free-of-charge 24 hours/day from ICI Americas, Inc 1-800-327-8633) associated with likelihood of death:
   * 2 mg/L at 2 hrs
   * 0.9 mg/L at 6 hours
   * 0.1 mg/L at 24 hours

GENERAL TREATMENT

1. Controversial:
   * NO specific antidote or therapeutic regimen has been proven to work

2. Antidotes:
   * steroids, n-acetylcysteine, vitamin E, ascorbic acid, other antioxidants, have been tried in animals without success

3. Low oxygen environment:
   * no evidence it's effective, but maintenance of pO2 at or around 60 mm recommended by most, since hyperoxia may enhance oxidation

GUT DECONTAMINATION

1. Best outcome related to prevention of GI absorption:

* presence of food in stomach associated with survival
* rapid administration of binding agent such as activated charcoal, fuller's earth, bentonite
* unclear if added emetics are effective - may be harmful
* unproven usefulness of whole gut irrigation

ENHANCED ELIMINATION

1. Forced diuresis:
   * no evidence of added benefit over normal urine flow

2. Hemodialysis & hemoperfusion:
   * case reports of survival despite lethal levels
   * remains controversial
   * if performed, charcoal HP should be started early and continued daily for several hours each day

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