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Adios Azinphos-Methyl, Farewell Phosmet

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Within a year after the August 1996 passage of the Food Quality Protection Act (FQPA), the backslapping giddiness accompanying this legislative compromise between agricultural interests and environmental advocacy groups dissipated to consternation that perhaps all was not as it seemed. Agricultural groups pointedly accused the EPA of dismissing "sound science." They believed EPA was showing an increasing propensity to curtail uses of OPs. Meanwhile, environmental advocates accused the EPA of lacking sufficient science about OPs. They suspected the agency was not faithfully and fully implementing the provisions of the FQPA.

Five years after the FQPA's coming-out party, the scorecard reveals that OP insecticides increasingly are becoming relics of the past. But ironically, the specific mandates of the FQPA to protect consumers, especially infants and children, may turn out to be the least of the reasons for the flight of the OPs. While the illusion of excessive dietary exposure whipped up astonishing antagonism, the issues that may prevent practical use of OPs are turning out to be worker exposure and ecological concerns. The latest casualties illustrating this point are the orchard favorites azinphos-methyl (formulated as Guthion) and its cousin phosmet (formulated as Imidan).

How We Got From There to Here

Before considering the gory details of the attack on Guthion use in orchards, a bit of history is in order. The present state of affairs represents a convergence of a recently settled lawsuit against the EPA and the application of older amendments to the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the overarching statutory authority for pesticide regulation.

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Before the FQPA required EPA to reassess all pesticide tolerances by the year 2006, the agency was already engaged, albeit very slowly, in re-registration of products registered before 1984 as required by FIFRA and its periodic amendments. But re-registration encompassed more than just estimating dietary exposure and approving tolerances. Chief among the additional considerations during re-registration were the provisions of a 1972 mandate titled FEPCA (the Federal Environmental Pesticide Control Act). FEPCA broadened FIFRA's myopic attention on human health and food residues to include worker exposure and ecological effects. FEPCA also gave rise to the classification of pesticides as either "general" or "restricted-use" products and brought about requirements for continual pesticide applicator training and licensing for application of restricted-use products. Concern for worker health was re-emphasized with implementation of the Worker Protection Standard (WPS) in 1994. Today, when EPA releases a RED (Registration Eligibility Decision Document), risks to workers and the environment are duly characterized (1).

During 1999, the advocacy group known as the NRDC (National Resources Defense Council) sued EPA over its failure to quickly implement all of the provisions of the FQPA. Specifically, NRDC based its case on EPA's reluctance to conduct cumulative risk assessments (CRAs) of OP insecticides (2). In March 2001 the Federal court hammered out a consent decree between EPA and the NRDC in which EPA was mandated to faithfully carry out the provisions of the FQPA by pushing forward a CRA of OP insecticides. EPA finally released a very comprehensive draft CRA in December 2001 (3). What may have escaped the casual observer's notice is that two little lines of this multi-page decree have enormous impact. They essentially broaden the scope of FQPA from consumer safety to worker and ecological protection. The consent decree of March 2001 commits EPA to conduct worker and ecological risk assessments.

Guthion in the Diet

The FQPA mandated that EPA re-evaluate all food residue tolerances for all pesticide products with special attention to five principle considerations: potential sensitivity of infants and children, potential to cause cancer, potential to affect the endocrine system adversely, aggregate exposure, and cumulative exposure. Despite being considered a very hazardous OP (Table 1), azinphos-methyl (AZM) did not trigger any concerns with regard to any of the principal considerations of the FQPA. Nevertheless, early assessments of dietary exposure to AZM residues led EPA to conclude that consumer exposure was excessive.

Refined assessments of exposure based on actual field residues and monitoring results from the USDA Pesticide Data Program (PDP) eventually muted concerns over chronic (daily lifetime) exposure, but acute exposure to infants and children was still deemed excessive (Table 2, composite apple residues). Bear in mind that acute dietary risk characterization is very conservative because probability modeling is used to estimate the 99.9^{th} percentile of exposure for different population subgroups (e.g., infants, 1-6 year olds, teenagers, etc.).

(Tables 1 and 2 follow. Text resumes on page 4.)

Table 1

Dose-response parameters for AZM and phosmet insecticides (mg/kg/day unless otherwise stated).

	Azinphos-Methyl	Phosmet
Acute Toxicity Parameters		
Acute Oral LD50 (rat)	4.5	113
Acute Dermal LD50 (rabbit)	>2000	>5000
Acute Inhalational LC50	>0.21 mg/L	>0.152 mg/L
RfD for Consumer Risk Characterization		
Acute RfD	0.0033	0.045
Chronic RfD	0.0015	0.011
Toxicity Parameters for Workers' Short-Term Exposure		
NOAEL for Dermal Toxicity	0.56	15.5
NOAEL for Inhalational Toxicity	0.32	4.5
Toxicity Parameters for Workers' Intermediate-Term Exposure		
NOAEL for Dermal Toxicity	0.36	1.1
NOAEL for Inhalational Toxicity	0.32	1.5

Table 2

Risk characterization for dietary exposure to azinphos-methyl with apple composite residues and single serving residues [1/]

	Apple Composite Residues		Single-Serving Apple Residues	
Population Group	**Exposure**	**% RfD**	**Exposure**	**%RfD**
U.S. Population	0.001781	59	0.001285	43
All Infants < 1 yr	0.003003	100	0.002504	83
Children 1-6 yrs	0.003913	130	0.002403	80
Children 7-12 yrs	0.002704	90	0.000329	53

1/ Exposure (mg/kg/day) is compared to the acute reference dose (RfD) of 0.0033 mg/kg/day and expressed as a percentage of the RfD. Percentages less than 100% are interpreted as a reasonable certainty of no harm. Data were based on the revised draft RED (1999) and interim RED (2001) for AZM; both can be downloaded from http://www.epa.gov/pesticides/reregistration/status.htm

In its revised draft RED issued in 1999, EPA agreed to re-register AZM, but the agency required some changes in use patterns and a lowering of tolerances from 2 parts per million (ppm) to 1.5 ppm. Because residues hardly ever exceeded the tolerance, exposure was not really mitigated. However, the amount of permissible AZM use in one season was reduced. Finally, EPA said it would revisit registration of AZM within two years to determine whether exposure had been reduced.

Environmental advocates expressed concern that commodities eaten fresh like apples are consumed individually, while residues have traditionally been determined by blending together numerous apples to yield a composite average concentration. Owing to variations in spray coverage, the potential existed for individual apples to have residues far exceeding the composite average. As a result of this concern, EPA began demanding registrants to consider residues on individual pieces of fruit. The USDA-PDP started monitoring single servings of apples, pears, and raw potatoes (http://www.ams.usda.gov/science/pdp/index.htm).

EPA revisited dietary exposure to AZM by examining single-serving apples. Apples disproportionately influence the dietary exposure picture, as children consume a large amount relative to their body weight when compared to adults. Further, AZM is used on nearly 75% of U.S. apple acreage. If, as hypothesized, single-serving residues are extraordinarily high, then one would predict that acute dietary exposure would appear even more excessive. Ironically, EPA concluded in its most recent revision of the AZM RED, known as the interim or IRED (4), that dietary exposure based on single-serving analyses was even less than that estimated from composite residue data (Table 2, single-serving apple residues). Indeed, EPA claimed that dietary exposure to AZM was no longer a concern. (After that exercise, don't be surprised if EPA no longer requires single-serving data for dietary exposure assessments!)

AZM's Days Are Numbered

Despite relief from concerns about dietary exposure to infants and children, EPA placed AZM on the chopping block, essentially suspending the forty-three registered crop uses (4). For eight of the uses (apples and crabapples, pears, sweet cherries, blueberries, caneberries, Brussels sprouts, nursery stock, and southern pine seed orchards), EPA determined that benefits outweighed risks and decided to issue a time-limited registration of four years. In other words, the apple, sweet cherry, and pear growers have a four-year reprieve, but then the AZM tolerances will be revoked. EPA was able to take benefits into consideration because worker and ecological risks, not dietary risks, were the drivers behind EPA's regulatory decision to not re-register AZM. The FQPA allows no considerations for benefits, but worker and ecological considerations are mandated by FEPCA and are therefore outside of the mandates of the FQPA.

Common sense alone dictates that orchard workers will be exposed to AZM, but should workers be held to the same margins of safety that we bestow on infants and children? In other words, how much risk is a worker allowed to bear and is it unreasonable?

Worker Worries

The process of determining risks to workers is essentially the same as for consumers, but routes of exposure are different. For example, dietary and drinking water exposure are irrelevant. Workers are exposed during mixing, loading, and application of pesticides through either the skin (dermal) or through breathing (inhalational). Thus, EPA prefers to use the no observable adverse effect levels (NOAELs) from rodent dermal and inhalation short- and intermediate-term exposure studies as the hazard benchmark for assessing the degree of worker exposure (Table 1). For OP insecticides, the NOAEL has been almost exclusively based on the most sensitive effect: inhibition of the nerve-signal modulating enzyme acetylcholinesterase that is found in red blood cells as well as in nervous tissue.

For any cropping system, EPA examines exposure based on work activity, length of exposure, and use of various kinds of PPE (personal protection equipment) and engineering controls (closed mixing/loading systems and enclosed tractor cabs). Exposure information comes from a combination of field experiment data (if available) and a database called PHED (Pesticide Handler Exposure Database). PHED consists of worker exposure studies collected over many years from industry. The data include unit exposures for different types of worker activities. The specific chemical being assessed is less relevant than the application rate, acres treated, and length of time worked.

For post-application exposure, such as would occur for tree proppers, fruit thinners, and hand harvesters, the residues on leaves that are easily transferred to skin (called dislodgeable foliar residues, DFRs) are estimated by extracting leaves with water containing a surfactant. Although the major cropping systems are represented in the PHED, the effects of specific changes in application or harvesting practices on unit exposure parameters and/or DFRs must be estimated to reflect currently relevant or proposed practices.

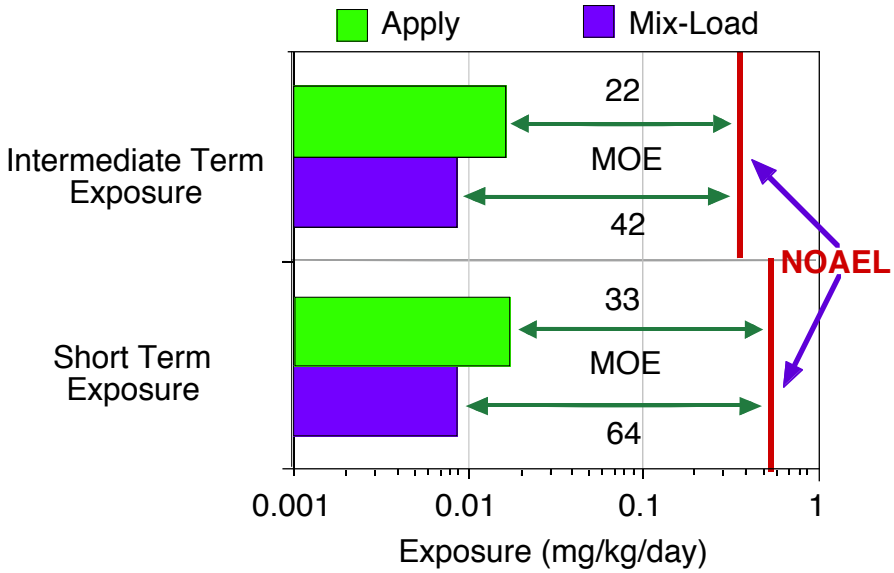
The calculated exposures for the different worker scenarios are compared to the dermal and inhalational NOAEL for short-term (1-7 days) and intermediate term (one week to several months) exposure (Table 1). The ratio of the NOAEL to the exposure is called the margin of exposure (MOE). MOEs less than 100 require exposure reduction.

For each registered AZM use, EPA calculated that many worker activity scenarios had MOEs less than 100. For example, MOEs for mixing/loading and application of 1 lb AZM/acre in apples ranged from 22 to 64 (Figure 1). Pertinently, EPA concluded the risk could not be further mitigated because exposure scenarios already considered full PPE and maximum engineering controls.

(Figure 1 and Table 3 follow. Text resumes on page 7.)

Figure 1

Risk characterization of worker exposure to azinphos-methyl during mixing, loading, and application in apples.



Assumptions are 1.5 pounds of active ingredient per acre and maximum personal protection equipment and engineering controls (e.g., water soluble insecticide bags). The MOE is represented by the arrows between the NOAEL (heavy [red] vertical lines) and the magnitude of exposure (wide [green and blue] bars).

Table 3

Risk characterization for post application exposure of workers to Guthion. [1/]

DAT	Task	DFR ($\mu g/cm^2$)	Transfer Factor (cm^2/hr)	Exposure (mg/kg/day)	Short Term MOE
2	Propper	1.56	100	0.0178	31
2	Irrigation, Scouting, Weeding	1.56	1000	0.1783	3
2	Thinner	1.56	3000	0.5349	1
7	Harvester	1.26	3000	0.4320	1
14	Harvester	0.93	3000	0.3189	2
21	Harvester	0.7	3000	0.2400	2

1/ DAT = days after treatment; DFR = dislodgeable foliar residues; Transfer Factor = surface area of skin exposed during one hour of activity; Exposure = (DFR x Transfer Factor x hours worked [8]) / body weight [70 kg]; MOE = margin of exposure calculated as the ratio of the NOAEL (0.56 mg/kg/day for AZM) relative to the exposure.

EPA was especially concerned about post-application practices because they yielded the lowest MOEs based on current restricted-entry intervals (REIs) (Table 3). REIs are the number of days after an application before a worker can enter the treated area. They are essentially exposure reduction standards and ideally should coincide with MOEs of 100 or greater. To achieve an MOE of 100 in apples, REIs for propping, scouting/irrigating, and thinning/hand harvesting would have to be set at 32, 79, and 102 days, respectively. Compared to the current REI of two days for propping, scouting, and irrigating, and fourteen days for thinning and harvesting, the acceptable risk REIs obviously would be impractical.

AZM Does the Regulatory Limbo

Eight crop uses received time-limited registrations because the benefits of AZM were determined to exceed the risks of adverse effects on workers even though MOEs were substantially less than 100 (4). In four years, the registrant, Bayer Corporation, will have to request an extension of the registration. Additionally, the time-limited registration required changes in the product label and submission of new data, such as the following (for use in apples):

- Limit maximum yearly use to 3.5 lbs per acre east of the Mississippi River and 4.0 lbs per acre west of the Mississippi;
- Increase REI to 14 days for all worker activities;
- Require closed mixing systems or water soluble bags and closed transfer systems for mixing/loading;
- Require enclosed cabs or maximum PPE for applicators;
- Prohibit aerial application;
- Add spray drift language;
- Orient nozzles on airblast sprayers inward;
- Add 25-foot no-spray buffer zones around permanent surface water;
- Add bee warning statement;
- Encourage development of Pest Management Strategic Plans (see *Et Tu, Phosmet?* below).

In addition to required label changes, Bayer will have to submit new study data, including:

- Biomonitoring study of worker harvesting and thinning activities that would measure both cholinesterase and AZM biomarker levels. Studies must be conducted in the Pacific Northwest, the Northeast, and California;
- Full fish life cycle toxicity study;
- Ground water monitoring;
- AZM usage information during the next three growing seasons;
- Information about alternative insecticides under development or commercialized;
- Exposure-reduction feasibility study of post-application use of protective gloves.

Reality Checks

The selection of an MOE of 100 for protection of workers is strictly a risk management decision. Risk management decisions are social, not scientific. An MOE of 100 is the same safety factor represented in the RfD that is applied to dietary risk characterization. While toxicology cannot dictate what a sound MOE should be for worker risk characterization, epidemiology can show the propensity for worker health effects to be associated with pesticide use. Worker activities associated with MOEs less than 100 should have a greater probability of resulting in worker health effects than activities with MOEs greater than 100. One way to determine whether this hypothesis is valid is to examine the incidence of worker poisonings and place them into perspective with the number of applications.

Worker exposure and health effects incidents are tracked by state poison control centers, state health agencies, and the EPA. The resulting databases can be used to examine frequency of complaints about AZM. For example, in a 1985 cholinesterase surveillance study of over 500 workers in California (cited in Reference 4), 94 workers had marked cholinesterase inhibition (i.e., >20% inhibition compared to an individual's own baseline enzyme activity). Of these, 11% or 10 workers were definitively exposed to AZM. To calculate the incidence of worker exposure per application, consider that California grows nearly all of the United States' almonds, walnuts, and pistachios, which are heavily reliant on use of AZM. EPA had estimated that 289,000 pounds of AZM were used yearly on these crops. At the recommended rate of application, a total of almost 130,000 acres would have been treated. If we assume conservatively that a worker could treat five acres with one tank full of AZM mixture, then 25,980 tanks of AZM would have been mixed just to treat these tree nuts. Because each tank load has to be prepared anew, the incidence rate of workers with excessive cholinesterase inhibition per tank load would be 10 divided by 25,980 or 0.000398. So in 1985, approximately one worker was overexposed for every 2500 tank mixes (or individual applications) of AZM. Is that an excessive risk, as EPA's calculations of MOE suggest? To reiterate, such a judgment is purely a social decision, not a scientific one.

Similar estimates of worker health effects incidence rates can be calculated for other crops on which AZM is used, such as apples. EPA stated in the AZM IRED that about sixteen cases of AZM poisonings are reported each year. As a worse case, we will assume that all of these poisonings were related to apple production. EPA's estimates for AZM use are 890,000 pounds; at an application rate of 1.5 lbs/acre, the equivalent of 593,000 acres of apples would be treated. If five acres can be treated with each tank full of spray mixture, then 118,667 applications (i.e., refilled spray tanks) are made during a growing season. Thus, one worker reports AZM symptoms for every 7,690 applications.

Because post-application workers were determined to have the greatest risk by virtue of their estimated exposure being very close to the NOAEL, it is instructive to estimate the incidence of poisonings relative to the number of workers engaged in harvesting. EPA estimated that 45,000 workers are engaged in picking apples nationwide. If all sixteen poisoning incidents reportedly due to AZM each year occurred with apple harvesters (an extremely conservative proposition, as apples account for only 40% of AZM use), then the incidence rate is 0.04%. In other words,

one out of about 2500 apple pickers could be reporting symptoms from AZM exposure each year. While excessive exposure to any pesticide is always unacceptable, reality dictates that farming is like any other business. So, a pertinent question is to ask how the estimated injury incidence rates compare to other industries.

The Bureau of Labor Statistics (BLS) of the U.S. Department of Labor compiles a database of injury and illness incidence rates for all major industries in the United States. (Their Internet URL is http://stats.bls.gov/iif/oshsum.htm.) The illness incidences are broken down by causes, including the separate categories of "poisoning" and "respiratory conditions due to toxic agents." The BLS estimated that 169,400 workers were employed for all of the fruit and tree nut industries during 2000, and further estimated a poisoning incidence rate of less than 0.05 per 10,000 workers. Because labor departments are not as efficient at collecting on-farm pesticide incidents data as agencies that specialize in collecting that data, the average sixteen poisoning incidents from AZM can be prorated to all fruit and nut tree employees, thereby yielding the much higher incidence rate of 0.94 (or about one person reporting poisoning out of 10,000 workers). For a comparison to other industries, let's choose the chemicals and allied products manufacturers because those workers also handle hazardous chemicals and are thus likely to have higher than average exposures. For all types of chemical manufacturing, the poisoning incidence rate was 0.3 per 10,000 workers, but it varied by specific industry. For example, workers in the agricultural manufacturing industry (51,000 workers) had an incidence rate of 1.3. Surprisingly, workers in the innocuous-sounding medicinals and botanicals manufacturing industry (28,200 employees) had an incidence rate of 3.4. So, in comparison to other workers that have definitive chemical exposures, fruit and tree nut workers do not appear to be experiencing an unusual incidence of poisonings owing to AZM use. To reiterate an earlier point, everyone wants to avoid worker illnesses, but farm workers do not seem to be getting sick at extraordinary rates in comparison to other workers who handle chemicals.

Et Tu, Phosmet?

Phosmet is another OP insecticide that is currently crucial to the orchard industry. Like AZM, its benefits exceed its risks. By both oral and dermal exposure, phosmet is significantly less acutely toxic than AZM and the selected RfDs were nearly tenfold greater (Table 1). Consequently, the revised draft dietary risk assessment dispelled any concerns about excessive acute and chronic exposure (5). Unlike AZM, however, phosmet does have residential uses, including pets, household ornamentals, and residential fruit trees. But according to its IRED, aggregate exposure assessment still raised few concerns about excessive consumer exposure. The only problem areas involved toddlers touching treated dogs and homeowners treating backyard fruit trees with a hand wand sprayer. Phosmet's registrant, the Gowan Company, has requested voluntary cancellation of all residential uses, thus making moot any concerns over aggregate risk.

For thirty-three registered crop uses, worker exposure did not exceed EPA's levels of concern if appropriate PPE was used. However, nine of the registered uses posed post-application worker exposures unacceptable to EPA. The crops included apples, crabapples, apricots, high-bush blueberries, peaches, pears, plums/prunes, nectarines, and grapes. Specifically, EPA

determined that the MOEs for post-application exposure were close to 10 at the current REI of twenty-four hours. Not until thirty-four days after application did MOEs rise to 100.

Because phosmet, like AZM, had extraordinarily high benefits for use on fruit trees, EPA decided to issue a time-limited re-registration for the nine uses presenting excessive post-application worker exposure. EPA forged an agreement with Gowan Company to consider re-registration after five years, but the REIs would be extended from the interim three days to 13-29 days. For example, in 2006, phosmet could only be used if the REI for apples was extended to 13 days for a 1.5 pound per acre application (lbs/A) or 28 days for the 4 lbs/A rate. In addition, Gowan agreed to conduct a cholinesterase monitoring study with post-application workers, as well as to continue providing EPA with information about phosmet usage and benefits.

Finally, during the time-limited registration, EPA encouraged growers and commodity organizations to develop or expand Pest Management Strategic Plans (PMSPs). PMSPs are stakeholder-driven, commodity-specific plans that identify current and emerging pest management practices. PMSPs also state a commodity's priorities for research, regulatory activities, and education/training programs to support transition to alternative pest management practices. (See http://www.pmcenters.org for more information and see related article in this issue regarding an upcoming opportunity to learn about PMSPs in Spokane, Washington, April 9, 2002.)

It Ain't Over Until the CRA Sings

Concerns over excessive worker exposure to OPs, especially to fruit thinners and harvesters, seems to have supplanted concerns about consumer risk now that methyl parathion, chlorpyrifos, and diazinon uses have been significantly curtailed. The time-limited registrations of AZM and phosmet are prime examples of OP uses that will be nixed unless the registrants generate new information and follow all agreements about REIs and other risk mitigation procedures.

It is important to remember a critical difference between consumer risk and worker exposure: when assessing the latter, EPA can weight benefits against risk. AZM and phosmet are the only effective codling moth control products on the market. Even growers who are using the biologically friendly, pheromone-based mating confusion systems require at least one insecticidal cover spray to knock down moth populations for optimal control. AZM is currently a critical pesticide for control of cherry fruit fly because phosmet poses a risk of phytotoxicity to sweet cherries (5). The benefits of AZM and phosmet are clear, and will lessen only as newer, reduced-risk pesticides with activity against codling moth and cherry fruit fly join the marketplace.

But before reconsidering benefits, EPA will revisit consumer risk. In the preliminary CRA for OPs, EPA declined to state specifically what the results meant for the future of the OPs (2). EPA could conceivably make the decision to further restrict those OPs that are driving the comparatively higher dietary exposures of children. As the favorite insecticide for children's

favorite fresh fruit, AZM could be vulnerable to further restrictions even if worker exposure concerns are eventually resolved.

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