Toxicology of AHS Important Chemicals

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Toxicants, including agricultural chemicals, following either acute or chronic exposure may give rise to more than one toxic endpoint. Understanding acute toxicity to target organisms is important in agricultural, public-health, and military applications while understanding acute toxicity to nontarget organisms, particularly humans, is important in safe handling and use regulation. Knowledge of environmental effects is of importance for the preservation of ecosystems. However, understanding of chronic effects in humans is critical to the realization of the goals of the Agricultural Health Study (AHS).

Mode of toxic action should not be thought of as a defining chemical event but rather as a cascade of events that starts with exposure and ends with the expression of a toxic endpoint. Intermediate steps include absorption, transport, metabolic activation or detoxication, interaction with cellular macromolecules, as well as excretion and repair. These steps may be reversible or irreversible and may vary between species, organs, and individuals. Until recently most of the toxicological input into human health risk analysis has been based on studies of surrogate animals [1,2]. However, as summarized in the following presentation, it has recently become possible to conduct relevant human studies. Human studies not only strengthen risk analysis in general but are essential for understanding of several aspects that cannot be investigated using surrogate animals, including the estimation of variation between individuals and subgroups in the population, and the definition of metabolic interactions specific to humans.

The chemicals listed below are selected primarily on the basis of epidemiological associations emerging from the Agricultural Health Study and other epidemiological studies of agricultural chemicals. It has been slightly amplified based on considerations of high volume of use and will need to be further modified both on this basis and by adding chemicals subsequently found to be relevant in the Agricultural Health Study.

The mechanism of acute toxicity of the *organophosphorus insecticides* (OPs), chlorpyrifos*; coumaphos, DDVP, diazinon, fonofos*; and phorate* in both target and nontarget species (including humans) is inhibition of acetylcholinesterase, giving rise to accumulation of acetylcholine in the synapse. With the exception of DDVP, all of these OPs must be activated by cytochrome P450 (CYP) to their oxons (potent anticholinesterases). Little is known of their chronic toxicity but as a result of oxidative desulfuration, they are potent irreversible inhibitors of steroid hormone and xenobiotic metabolism, and they are also believed to interact with neuroreceptors.

The *carbamate insecticides*, carbaryl* and carbofuran*, are also inhibitors of acetylcholinesterase. However, unlike phosphorylation, carbamylation of acetylcholinesterase is reversible. As a result, carbamate insecticides are generally less acutely toxic than organophosphorus insecticides and recovery is more rapid. Activation to a reactive metabolite is not required and, again, little is known concerning chronic effects.

Both OPs (chlorpyrifos,* diazinon) and carbamates (carbaryl, carbofuran) have been associated with lung cancer in early results from the AHS.

Permethrin* is a widely used *pyrethroid* insecticide that shows a number of interactions in the nervous system, the most important to its acute toxicity being interaction with sodium channels. The low mammalian toxicity of permethrin is attributed to its rapid metabolic clearance. Dieldrin and related *cyclodiene* insecticides owe their acute toxicity to their ability to interact with the picrotoxin-binding site of the GABA-receptor-ionophore complex. Dieldrin is also known to have reproductive effects, to be a CYP inducer, and to be carcinogenic to mice. Although the use

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*The human metabolism of these chemicals has been investigated by the authors and will be discussed in the following presentation.

of dieldrin and other cyclodienes has been banned in the USA for a number of years, because of their stability in the environment, there is still considerable exposure of the human population to low levels of these chemicals.

The *fumigant*, methyl bromide, is known to be highly toxic to humans. It is a blistering agent, a neurotoxicant, and a cardiotoxicant. It is a potent electrophile, reacting with nucleophilic centers in biological macromolecules. Although it is clearly a genotoxicant, its carcinogenic potential had been a matter of controversy. Early results from the AHS, however, associate methyl bromide with prostate cancer.

In addition to methyl bromide, a number of other pesticides are also associated with prostate cancer in those members of the AHS cohort with a family history of prostate cancer but not in those without this risk factor.

The insect *repellant*, DEET*, appears to be a safe chemical, exposure of some 75,000,000 people/year in the United States alone having resulted in only a small number of anecdotal accounts of injury. Since it is metabolized by CYP and this metabolism is inhibited by chemicals likely to be involved in coexposure scenarios, such as chlorpyrifos, it has some potential for metabolic interactions that may affect toxicity.

The *chloroacetamide herbicides*, alachlor*, acetochlor*, butachlor*, and metolachlor* have been associated with cancers at various sites in rodents as follows: acetochlor—nasal epithelium, thyroid, liver; butachlor—stomach; alachlor—nasal epithelium, thyroid, stomach; metolachlor—liver. The DNA reactive intermediates are quinone imines generated by metabolic pathways that involve CYP isoforms as well as arylamidase. However, since the metabolism of these chemicals varies between rodents and humans, it is not clear how these results may be extrapolated to humans.

Although little is known about the metabolism of the *substituted aromatic herbicides* dicamba and pendimethalin in humans or surrogate animals, they are of low acute toxicity to mammals and not previously known to be carcinogenic. However, early results from the AHS associate these chemicals with lung cancer.

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