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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

July 14, 1997

SUBJECT: Duration of Aldicarb's Effects

TO: Jack Housenger
Deputy Division Director
SRRD (7508W)

FROM: William F Sette, Ph.D.
Toxicologist
Science Analysis Branch

THRU: William L Burnam, Chief
Science Analysis Branch
Health Effects Division (7509C)

The purpose of this memo is to provide a formal written response to the issue posed in earlier discussions in HED and with SRRD and with the registrant regarding the questions of:

How long should EPA regard the effects of acute exposure to aldicarb as lasting?; and derivatively, then,

Over how long an interval of time it is appropriate to use to define an acute consumption episode for commodities?

In my judgment, review of the available data support 8 hours as a reasonable best estimate of the duration of aldicarb's effects and so, also, the acute eating interval.

Rationale

First, residues on single commodities are the basis for our concern. You could look at this as giving the baby half an orange now and the other half after lunch, but it's still one orange. So whatever data anyone uses, it should square with one commodity at one "episode". The main issue, then, is how long may that "episode" be?

A number of the critical controlled human studies and case series provide relevant data on this topic in terms of the duration of illness and on the time course of cholinesterase inhibition. These human data involve single exposures to

contaminated commodities or to experimental doses, so there is no systematic data on whether someone exposed more than once in a given day might reasonably be expected to show cumulative response.

Similarly, among the animal studies, there are acute data, and repeated exposure data, but no examination of within day repeated exposures.

In Rhone-Poulenc's 1992 study, adverse effects were reported to generally to have a duration of 6 hours or less. Similarly, in the other controlled human study, effects and ChEI were reported to have been resolved within 6 hours of exposure.

But in some of the case reports, e.g., Goes et al. (1980), on illness duration of 14 cases, shows 2 of 14 cases with illnesses lasting 12 hours, and another, an 80 year old woman, was hospitalized for 24-36 hours, but the time of cessation of her illness was not noted. Hirsch et. al. 1987 note recovery generally within 8 hours.

With respect to ChE inhibition, Rhone-Poulenc's human study from 1992, the best available data set, does show statistically significant blood cholinesterase inhibition 1-6 hours after exposure for 3 of 4 doses tested in plasma and (most consistently) for the 2 highest doses tested in RBCs. In addition, EPA expressed some concerns in our review of that study regarding the red blood cell measures as potentially underestimated by on incomplete lysing of the red blood cells (leaving an incomplete red blood cell quantity in the supernatant for analysis).

Thus a cumulative response might well be anticipated within that period.

In summary, then, for the controlled studies and in most case reports, effects were resolved within 6 hours of exposure. For the best available cholinesterase data, overall evaluation found significant changes in blood ChE inhibition 6 hours after exposure with resolution in general by 8 hours after exposure, particularly at lower doses, which is where most concerns related to potential contamination of commodities lies.

In conclusion, an interval of 8 hours seems the best estimate of an interval where all effects would be recovered and where cumulative effects on ChE inhibition would not be expected.

NOTES

The data are tabulated below.

DOSE	1 HR	2 HRS	4 HRS	6 HRS	8 HRS	21 HRS
0.01						
M RBCS	X	X	X			X
M PLASMA	X	X				
0.025						
M RBCS	X	X	X		X	
M PLASMA	X	X	X	X		
F RBCS	X	X				
F PLASMA	X	X	X			
0.05						
M RBCS	X	X	X	X		
M PLASMA	X	X	X	X	X	X
F RBCS	X	X	X			
F PLASMA	X	X	X			
0.075						
M RBCS	X	X	X	X		
M PLASMA	X	X	X	X	X	X

With respect to inhibition of ChE, significant inhibition of RBCs after 6 hours were noted at the 2 highest doses, at 8 hours after 0.025, and after 21 hours at 0.010 mg/kg. While the effects at the two lower doses were discontinuous in that earlier measures were not statistically significantly different, there are clearly effects at 6 hours.

Thus, it seems prudent to be concerned for repeated exposures within 8-12 hours of one another. This I base on the facts that in the ChEI data, at 8 hours the differences seen were

no longer statistically significant, and that in Goes et al., the 2 instances of effects longer than 6 hours were given as lasting 12 hours.

Second thoughts: both Goes and Hirsch mention 12 hours; but scotland effects are clearly? shorter in duration.

What of UC 71 in terms of duration?
All recovered within 6 hours of exposure.
Or Goldman?

What are we saying here? That any food eaten over 8 vs 12 hours should be regarded as one meal or exposure? I think that's it.

7/10: Examination of the raw ChE data from the Scotland study support 8 hours as a reasonable judgment of time of essentially complete recovery of ChEI in plasma and RBCs.
Certainly effects were recovered by then.