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MEMORANDUM

SUBJECT: **Profenofos**: Review of Acute and Repeated Exposure Comparative
Cholinesterase Study Protocols

TO: Terria Northern
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Special Review and Reregistration Division (7508C)

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THRU: Developmental Neurotoxicology Protocol Review Committee
Health Effects Division (7509C)

and
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Alberto Protzel 6/27/02

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Chemical: Profenofos
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ACTION: The purpose of this memo is to review draft protocols submitted by Syngenta for studies to be conducted at Central Toxicology Laboratories for the assessment of cholinesterase activity in adult and immature rats following acute or repeated exposures to Profenofos.

CONCLUSION: These protocols are partially adequate for the assessment of comparative cholinesterase activity data as specified in the EPA Data-Call-In (DCI) for adult and developmental neurotoxicity (DNT) studies on the organophosphate (OP) pesticides (issued September 10, 1999) with the following exceptions and comments. The protocols do not assess dams and fetuses on GD 20. Forty two day old rats are proposed as young adults, but EPA would prefer that they be at least 60 days old. Pup allocation for repeated exposure should not use 5 pups/sex from the same litters, but allocate pups, e.g. one/sex/litter as is proposed for the acute study, to avoid confounding litter and dose.

Introduction

At the request of the Agency, the registrant, Syngenta, has submitted draft protocols (dated February 4, 2002) for studies that were designed to assess cholinesterase activity in immature and young adult rats following acute or repeated exposures to Profenofos. The studies described in this submission are intended to satisfy the requirement for comparative cholinesterase data as specified in the EPA Data-Call-In (DCI) for adult and developmental neurotoxicity (DNT) studies on the organophosphate (OP) pesticides (issued September 10, 1999). Additional instructions provided to the registrant in a document entitled *Guidance on Cholinesterase Measures in DNT and Related Studies (10/29/01)* form the basis for the review of the comparative cholinesterase protocols. A summary of the EPA guidance regarding the subjects and times for measurement of cholinesterase activity is given in the following table:

Summary of EPA Guidance on Required Cholinesterase Measures	
Study	Populations
Main DNT study	1. PND 4 (pups) 2. PND 21 (pups and dams)
Maternal GD 6-20 study	1. GD 20 dams 2. GD 20 fetuses
Sensitivity study	<u>Acute doses:</u> 1. Pre-weaning pups (both sexes); a) Early-Mid lactation [no later than PND11]; b) Late lactation [7-10 days after first time point, no later than PND 21]; 2. Young adults (both sexes).
	<u>Repeated doses:</u> 1. Pre-weaning pups -- exposure beginning during early lactation, with a duration of 7-10 days (starting no later than PND 11, e.g., PND 11-21), with ChE evaluations after dosing on last day of exposure; 2. Young adults (both sexes) -- repeated dose exposure using duration and doses as for pre-weaning.

The following discussion presents the Agency response to the draft protocols.

Cholinesterase measures in the main DNT study and in GD 20 dams and fetuses

The protocol for the main DNT study has been previously reviewed by the Agency. The Agency guidance (10/29/01) recommends the measurement of cholinesterase activity during the course of the DNT study in dams and pups on GD 20, in pups on PND 4, and in dams and pups on PND 21. The previously reviewed protocol proposed testing of pups on PND 0 prior to first suckling, which may be a surrogate for GD20 measures in pups, but did not propose any corresponding measures in dams. These protocols also fail to mention such measures in dams.

Cholinesterase measures following acute exposure to adult and immature rats

The acute protocol proposes assessment of 5 pups/sex/dose on PND 12 and 22, and young adults on day 42. This is consistent with the guidance document. Five pups/sex/dose should generally be acceptable if the sensitivity of the cholinesterase assay is adequate, e.g., CVs of roughly 20% or less. However, for data on young adults, EPA is concerned that 42 day old rats may not be fully mature with respect to enzyme systems and so rats at least 60 days old are preferred.

Cholinesterase measures following repeated dose exposures to adult and immature rats

The protocol will have 8 litters and dams and proposes to allocate 2 litters to each treatment group, from which a total of 5 male and 5 female pups will be drawn. This scheme is undesirable since it will confound litter source with dose; that is, differences seen between dose groups may be a function of effects due to being from the same litter, rather than from the dose itself. It is preferable, as is proposed in the acute protocol, to allocate one pup/sex/litter to each of the different dose groups, so that animals from all litters are in each dose group.

The protocol proposes dosing of groups of 5 pups/sex/dose for 10 days starting on PND 12 with assessment of ChE on PND 21, and dosing groups of 5 young adults/sex/dose starting on PND 42 for 10 days with assessment of ChE on PND 51. Detailed clinical observations will be made to dosed animals prior to dosing and after exposure at the time of peak effect (undetermined) on each dosing day. Body weights will be recorded prior to dosing. This is consistent with EPA recommendations; Syngenta is correct in defining 10 days of dosing as PND 12-21 or PND 42-51 inclusive, which we hope clarifies this issue, as was requested.

As mentioned above, 42 day old rats may not be fully mature with respect to enzyme systems relevant to metabolizing OPs. Day 60 or later would be preferable.

Other Comments

Analysis of dose preparations

Homogeneity and stability of the test material should be tested and included in the study report, along with data on achieved concentrations.

Vehicle

The rationale for the proposed vehicle, carboxymethyl cellulose, should be identified.



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