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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

April 12, 2002
TXR 0050513

MEMORANDUM

SUBJECT: D281194: Tetrachlorvinphos (PC Code 083701)
Comparative Cholinesterase Study Protocol

TO: Demson Fuller
Special Review and Reregistration Division (7508C)

FROM: Susan Makris 4/12/02
Toxicology Branch
Health Effects Division (7509C)

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

and
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Toxicology Branch
Health Effects Division (7509C)

Alberto Protzel 4/12/02

cc: Michael Nieves, SRRD (7508C)
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Executive summary

A draft protocol for the assessment of comparative cholinesterase activity in adult and immature rats following repeated dietary exposure to tetrachlorvinphos (PC code 083701) was submitted by SRA International, Inc. This protocol is not considered 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). The proposed study design, in which the test substance is administered in the diet to the dams and/or pups, does not include an estimation of actual dose (mg/kg/day) to the offspring and will not allow a valid comparison of cholinesterase inhibition in the adult and immature populations following repeated exposures. In addition, the protocol does not 1) assess cholinesterase activity following an acute dose of tetrachlorvinphos, or 2) assess cholinesterase activity in GD 20 dams and their fetuses.

Introduction

At the request of the Agency, the registrant, SRA International, Inc., has submitted a draft protocol (dated February 18, 2002) for a study that was intended to assess cholinesterase activity in adult and immature rats following exposure to tetrachlorvinphos. The study described in this submission is 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 protocol. The EPA position regarding the optimal schedule for measurement of cholinesterase activity is summarized 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	Acute doses: 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).
	Repeated doses: 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.

In addition, as described in the guidance, 1) the time of peak effect should be determined for each age group and should be based upon cholinesterase inhibition and 2) it is important that doses be selected in a manner that allows characterization of the dose effect curves for all 3 compartments (i.e., plasma, erythrocyte, and brain).

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

Proposed study design

The draft protocol (Argus Research, Horsham, PA, Protocol 999-804) describes a study in which tetrachlorvinphos will be administered in the diet to P generation pregnant female rats (6/dose) and F1 generation males and females. The control rats will be maintained on untreated diet from lactation day 1-22, three groups will receive treated feed from lactation days 1-11 and three

groups will receive treated feed from lactation days 11-22. Maternal body weight and food consumption data will be utilized to calculate test substance intake. Blood samples will be collected for cholinesterase measures on lactation day 4 from control dams and dams that are treated from lactation days 1-11. Dams will be killed on lactation day 11 (for those treated from LD 1-11) or 22 (for those treated from LD 11-22); at the time of sacrifice, blood and brain samples will be collected for cholinesterase analysis. Two pups/sex/litter will be selected for sacrifice and cholinesterase measures (plasma, red blood cell, and brain) on PND 4, 11, or 22.

Comparison of responses following the comparable doses

The primary and most critical attribute for a test of comparative sensitivity is the ability to precisely define the dose to each animal on study. In the study proposed by the registrant, dose to dams is calculated from body weight and food consumption data. No attempt is made to measure dose to the pups. Without information on exposure, there is no quantitative basis for a comparison of response.

Cholinesterase measures following acute exposure to adult and immature rats

The proposed protocol does not include cholinesterase measures in adult and immature rats following a single exposure to tetrachlorvinphos.

Cholinesterase measures following repeated dose exposures to adult and immature rats

GD 20 dams and fetuses - The proposed protocol does not include an assessment of cholinesterase activity in pregnant dams and their fetuses.

Immature rats versus young adults - Although the proposed study design includes cholinesterase measures in dams and their offspring (at three ages) following repeated exposures of tetrachlorvinphos, the exact dose to each animal is not known.

Cholinesterase measures in the main DNT study

The protocol for the main DNT study is not under consideration at this time. However, the registrant is reminded that the current Agency guidance (10/29/01) recommends the measurement of cholinesterase activity during the course of the DNT study, as a tool in assessing the adequacy of postnatal dosing. Animals should be available for these cholinesterase assessments at PND 4 (culled pups) and at PND 21 (dams and extra weanlings).

Other comments

The proposed protocol could be useful in providing dose range-finding information prior to conducting a dietary developmental neurotoxicity study with tetrachlorvinphos, or in defining the adequacy of dosing for the main study.

Conclusion

The protocol submitted by the registrant is not considered adequate for the assessment of comparative cholinesterase activity data for tetrachlorvinphos, 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). The proposed study design, in which the test substance is administered in the diet to the dams and/or pups, does not include an estimation of actual dose (mg/kg/day) to the offspring and will not allow a valid comparison of cholinesterase inhibition in the adult and immature populations following repeated exposures. In addition, the protocol does not 1) assess cholinesterase activity following an acute dose of tetrachlorvinphos, or 2) assess cholinesterase activity in GD 20 dams and their fetuses.

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