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

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JUL 13 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Naled (DIBROM®) - Waivers and Protocols (Neurotoxicity Testing) in response to DCI.
ID #034401

Chemical: 586 (034401)
RD Record: S-412678/416180
HED Project: 2-1609

FROM: Irving Mauer, Ph.D., Geneticist
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TO: Brigid Lowery/Larry Schnaubelt, PM #72
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THRU: Karl P. Baetcke, Ph.D., Chief
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Registrant: Valent USA

Requests:

[A] Appraise registrant's requests to waive submitting data from two tests required in the newer neurotoxicity screen for organophosphate pesticides, specifically:

(i) a six-month ocular toxicity test in dogs;

(ii) a 90-day neurotoxicity assay in hens.

[B] Review and comment on protocols submitted to satisfy data requirements for acute (81-8) and 90-day (82-5) neurotoxicity testing in the rat. Both of these company submissions were prepared by registrant's consultant, Technical Assessment Systems (TAS) Inc., Washington, DC, in response to the Data Call-In (DCI) Notice of 09/91.

[A] Registrant's Justifications for Waiver Requests/TB CONCLUSIONS.

(i) Registrant bases the request to waive data from a 6-month ocular dog study (Gldn 85-7SS) upon having previously

(1)

submitted acceptable data (judged CORE-MINIMUM, HED Doc. # 005774) from a chronic oral gavage (capsule) tox. study in groups of Beagles (Gdln 83-1b) receiving 0, 0.2, 2.0 and 20 mg/kg of the technical (91.4% a.i.) daily for one year, performed by International Research and Development Company, (IRDC), Mattawan, MI (IRDC Study No. 415-044, Final Report dated 6/10/86). At doses up to the HDT (producing increasing decrements of cholinesterase inhibition, and other biochemical changes), no treatment-related ocular changes were recorded employing a number of standard ophthalmological/fundal observations (including indirect, as well as direct/slit-lamp examinations)[1], nor in gross or histopathological (light-microscopic) examinations. According to the registrant (as enunciated by the TAS consultant), "....If a significant treatment related change had occurred with respect to corneal thickness, it could be expected to be noted by slit lamp examination. Likewise, there was no suggestion of any treatment induced functional abnormality of any ocular structure or extraocular muscle based ~~opn~~ gross clinical or biomicroscopic evaluation."

Further, the registrant/TAS correspondent maintains that:

"Although electroretinography (ERG) was not performed in the chronic dog study, the relevance of applying this technique is generally considered to be primarily limited to clarification and corroboration of histopathologic findings. Since there was no histologic evidence of a treatment-related effect on the retina following one year of continuous treatment, a separate six month study for the main purpose of evaluating ERG patterns should not be necessary."

[A] TOXICOLOGY BRANCH CONCLUSIONS TO WAIVER REQUESTS:

The agency does not accept, on face value, either of the above assertions proposed as justification for waiving the expanded canine data set (including, but not limited to, ERG measurements) required by the newer neurotoxicity screen. Naled, as well as other organophosphates undergoing similar re-registration eligibility, will have to be considered carefully as a class, in order to generate a consistent policy approach for this potential toxicological effect(s). Since these newer data requirements do not immediately impact the registration status of naled, such testing can be deferred for up to one year.

The registrant also requests a waiver for submitting data from a "Subchronic (90-day) delayed neurotoxicity study in hens" (identified in the DCI the letter as "Guideline Requirement

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[1]But no electroretinographic (ERG) examinations (cf, DER #005774)

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82-5a, "90-Day Neurotoxicity Study in Hens," but in the NTIS printing of these Guidelines as "Gdln 82-6, 28-Day Study") based primarily on the following rationale:

(1) The most recent Neurotoxicity Guidelines [NTIS Publ # PB91-154617] indicates that a 28-day study is required only when an acute study yields a positive neurotoxic response. Valent does not believe that, in the case of Naled, a positive acute response has been demonstrated and, consequently, do not feel that the recent Data Call-In requirement for additional testing is justified.

(2) A recent study satisfying all requirements for an acute delayed neurotoxicity study in hens (Guideline Requirement 81-7) has recently been submitted to the EPA by Valent USA Corporation [Redgrave et al., Acute Delayed Neurotoxicity Study with Naled Technical in the Domestic Hen, Huntingdon Research Center (HRC) Report No. CHR 33/90539, 7/30/90, MRID No. 416307-01]. Following review of this study, the Agency has concluded (EPA Data Evaluation Record in OPP Memorandum from Irving Mauer to Lois Rossi/Brigid Lowery, April 5, 1991, Attachment 5) that while "no signs of frank delayed neurotoxicity (locomotor ataxia, depressed NTE) at the LD_{50}" were observed, the study did show "increased histopathological evidence of axonal degradation in spinal cord and peripheral nerves and significantly depressed brain cholinesterase." Valent disagrees with the Agency's conclusion that the level of axonal degeneration observed is, by itself, sufficient to indicate a positive delayed neurotoxic response.

(3) The same study has been reviewed by the California Department of Food and Agriculture (CDFA) and found to be complete and acceptable for filling the data requirement in this area (CDFA, Medical Toxicology Branch, Toxicology Study Evaluation Worksheet January 3, 1991, Attachment 6). In contrast to the EPA evaluation, CDFA reviewers concluded that, as reported, the study did not demonstrate a possible adverse health effect and "that Naled is negative for acute delayed neurotoxicity in hens."

(4) Valent's commitment under this Data-Call-In Response to produce a new 90-Day Neurotoxicity - Mammals study (Guideline No. 82-5(b)) will result in neurotoxicity data which, to a large extent, will fulfill the requirements for the 90-Day Neurotoxicity - Hen study (Guideline 82-5(a)). Further, the species used in the committed subchronic neurotoxicity study, the rat, is

considered more predictive of neurological impact of naled on man.

TOX. BRANCH CONCLUSIONS TO WAIVER REQUEST [A](ii).

Different experts in the field of neurotoxicity testing as practiced in experimental animal models differ widely as to which toxic responses have the potential to cause, or are related to, human health effects. This is classically exemplified by the very same disparity between the two reviewers cited in interpreting the results of the HRC acute study: The one (EPA), adopting a conservative approach in indicating a potentially adverse effect guided by evident histopathological evidence (axonal degeneration in spinal cords and peripheral nerves), and significantly depressed brain cholinesterase activity in the absence of other (classical) evidence of organophosphorus-induced delayed neurotoxicity (OPIDN), which customarily includes additional clinical signs (such as locomotor ataxia) and biochemical lesions (principally inhibition of "neurotoxic esterase", NTE); whereas the second (CDFA), discounted both the increased level of axonal degeneration and significantly depressed brain AChE activity. The Agency stands by its interpretation of a potential for OPIDN in hens in the acute assay, and recommends that this potential be conclusively assessed in a repeat-dosing schedule (either 28- or 90-day duration).

We also note that the registrant's intention to conduct phases of the Agency's new neurotoxicity screen in the rat as companion studies (see below for assessment of the protocols submitted).

[B] Developing Data: Registrant's Protocols/Agency Appraisals.

The registrant has submitted (via its consultant, Technology Services Group, TSG, Washington, DC) the following protocols for studies to be conducted by WIL Research Lab., Ashland, OH:

(i) "An Acute Neurotoxicity Study of Naled in Rats" [EPA-FIFRA Gdln 81-8SS]

(ii) A subchronic (13 Week) Neurotoxicity Study of Naled in Rats" [EPA-FIFRA Gdln 82-5(b)]

The registrant offers these as draft "generic" protocols for both range-finding and definitive tests in anticipation of possible modification and refinement at (future) meetings with appropriate Agency staff, to discuss dose-selection and other parameters consistent with meeting Agency requirements for acceptable studies.

TOXICOLOGY BRANCH CONCLUSIONS TO PROTOCOLS [B](i) and (ii)

We are pleased to receive the proposals for conducting a preliminary neurotox screen in rats and are prepared to meet with registrant principals and toxicologists (or agents) at a mutually agreed time and date. Please consult with appropriate SRRD-PMs.