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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Naled - Company Response Dated October 4, 1985 to Evaluation of Previously Submitted Data. Caswell #586

FROM: Irving Mauer, Ph.D.
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1-23-86

TO: William Miller, PM 16
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and

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THRU: Jane E. Harris, Ph.D.
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Toxicology Branch
Hazard Evaluation Division (TS-769C)

JEH 1/24/86

for WRS 2/5/86

Registrant: Chevron Chemical

Action Requested:

Comment on company response (October 4, 1985) to Toxicology Branch (TB) review of the previously submitted mutagenicity study, entitled:

> In Vivo Cytogenetics Study in Rats. Naled Technical (SX-1397), EG&G Mason Research Institute MRI-193-CCC-82-82. June 6, 1983. S-2167,

which was judged UNACCEPTABLE.

1-7-2

Background:

In its review of this in vivo cytogenetic assay, TB stated that no evidence of an "effective" or cytotoxic dose at the target tissue (bone marrow cells) was provided, despite the (oral) administration of an MTD to rats (review attached to Memo: Mauer to Miller, dated December 24, 1984, TB Doc. #004170). In the company response, Chevron provides comprehensive data from acute LD_{50} and range-finding studies to support dose selection at MTD levels (in males, calculated at 38.87 mg/kg, and in females at 61.7 mg/kg) close to LD_{50} levels (in males, calculated at 85.1 mg/kg, in females at 81.2 mg/kg). Clinical signs of toxicity noted in the main (cytogenetic) test included ataxia, dyspnea and oral exudates in all females treated at the HTD, 61.7 mg/kg (and death of two females), but no apparent toxicities in males at the HTD, 38.8 mg/kg. Sampling of bone marrow cells at 6, 24, and 48 hours after acute gavage (4 animals per sex per group) revealed no increased chromosomal damage in test groups over controls, nor any changes in mitotic indices or modal chromosome numbers.

TB Discussion/Appraisal of Company Response

Based upon the acute data submitted by Chevron, TB is satisfied that an MTD was administered to females, and a level close to the expected MTD to males, by the oral route. We also note that the citations to EPA Guidelines (OPTS, 1982/1983) and EPA's Gene-Tox Report (Preston et al., 1981) recommend the HDT give evidence of animal toxicity after acute administration, or some indication of cytotoxicity.

EPA-OPTS Guidelines for this type of assay ("HG-Chromo-Bone Marrow") also suggest a "repeated treatment schedule can only be applied if the test substance does not exhibit cytotoxic effects in the bone marrow at the doses used", since the chemical may be active [at the target site] only after repeated administration. This appears to be a logical approach considering that intervening toxicity (even to death) following acute oral administration may have prevented sufficient concentrations of test material (if any) reaching the bone marrow to be recorded as evidence of such transport. Such pharmacologic evidence in bone marrow cells sought could be alterations in modal chromosome numbers or perturbations of cell cycling (e.g., in mitotic indices).

In the study submitted, it was reported that the positive control, cyclophosphamide (25 mg/kg CP) by i.p. injection was cytogenetically active in the absence of reported toxicity. That

2

an appropriate route of administration be chosen for the test agent was also noted in the EPA Gene-Tox Report cited (Preston et al., 1981), which suggests intraperitoneal injection for acute dosage schedules, in order to simplify the estimation of the dose potentionally deliverable [to the target tissue]. According to recommendations by this expert panel, another route of administration (e.g., oral) may be desirable in supplementary studies, in order to approximate the anticipated route of [human] exposure.

Further, the Gene-Tox report strongly recommends demonstrating mitotic delay as a desirable physiological endpoint by multiple-sampling times. [It should also be noted that this expert panel rejected from its consideration any reports lacking sufficient dosimetry at the target tissue.]

Hence, several alternatives would appear to have been available to the investigators to assure a scientifically valid mutagenicity assay was performed, and not merely confirmation of oral LD_{50} values. The first would have delayed sampling surviving animals (at all dose levels) even beyond the final schedule reported (48 hr). A second would have chosen the same route of administration as the positive control used (CP). Another could have employed a repeat dosage schedule (e.g., 5 days) at lower dose levels (to obviate the acknowledged acutely toxic sequelae attending oral administration of this OP).

However, since the minimal requirements of regulatory guidelines were apparently complied with, reconsideration suggests the study be upgraded to ACCEPTABLE at the doses employed, based on compliance with the Agency's OPTS Health Effects Test Guidelines (as well as OECD).