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

6-12-91

JUN 12 1991

JUN 12 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Fenoxaprop-Ethyl

TO: Joanne Miller PM 23
Registration Division (H7505C)

FROM: Karen E. Whitby, Ph.D.
Section, II
Toxicology Branch II/HED (H7509C)

THRU: K. Clark Swentzel 6/6/91
Section Head
Toxicology Branch II/HED (H7509C)

and

Marcia van Gemert, Ph.D. 6/7/91
Chief, Toxicology Branch II/HED (H7509C)

and

William L. Burnam, Deputy Director 6/10/91
Health Effects Division (H7509C)

Caswell No. 431C

The intent of this memorandum is to clarify HED's position on the fenoxaprop-ethyl mouse carcinogenicity study.

With the current request for use on wheat, the concern is that there will be increased exposure to this chemical through wheat, meat and milk residues, especially to non-nursing infants whose entire food source may be milk. The TMRC for the present tolerances uses 1.2% of the RfD. If wheat, meat and milk were added to the TMRC for the general population, the TMRC would jump to 4.5% of the RfD. The TMRC for children aged one through six will be raised from 2.5% to 10.1%. For non-nursing infants, the exposure will go from 5.97% of the RfD to 10.5% of the RFD.

In the January 27, 1986 DER from Dynamac it was stated that an MTD had not been achieved in the mouse cancer study. In the December 15, 1986 memo from Edwards to Mountfort it was stated that the MTD had not been achieved, since the "highest dose tested in the mouse

carcinogenicity study of 40 ppm is only approximately 1/8th of the 315 ppm dose" (the 32 day feeding study dose in which kidney necrosis was seen in females - a dose perhaps a little high for the MTD, but somewhere within the correct range). There were no 90 day mouse feeding studies for determining a MTD. At that time the existing Toxicology Branch position paper on MTD for carcinogenicity studies (dated April 1986) was used to define the adequacy of dosages in this study. This MTD paper contained 7 levels of a decision tree. When this document was used to assess the need for repeating the chronic mouse study, the first 6 of 7 levels did not indicate that the highest dosage tested was adequate for use as an MTD. Level 7 allowed for a conclusion to be based upon comparison of a Margin of Safety (MOS) (calculated from the highest dose tested) with estimated human exposure.

In keeping with this, the MOS ratio was 4800 (assuming worst case exposure 0.05 ppm in 100% of the diet) which was well in excess of the suggested ratio of 1000 according to criteria level 7. As quoted from the Edwards memo "the mouse study is considered to be acceptable as long as residues remain very low, eg. 0.05 ppm or less. If the company wishes to have increased residue levels, the whole question of the adequacy of the study will have to be reassessed."

After an internal review by other parts of EPA, Dr. Theodore Farber (contributor and Branch Chief) revised the MTD document and made it publicly available through the NTIS in 1988. Much of the paper was similar to the first draft except that the entire tier decision process was eliminated.

Based upon current acceptance criteria, as stated in Subdivision F Guideline Reference No. 83-5 (Chronic Feeding/Oncogenicity in the Rat) December 24, 1989 pp C-121-122, the decision would have been to not grant the tolerance until an adequate mouse study had been delivered, or to grant registration conditional on submission of a new, well-designed mouse carcinogenicity study. At the time, however, not requesting another study seemed a reasonable alternative, since the residues were so low, and also it followed the logic set forth in the original (draft) MTD document.

In an attempt to view this issue from a different perspective and give our recently developed "Ersatz" Q_1^* Risk Assessment procedure a trial, a test run was performed using hypothetical data with a very high tumor incidence. The outcome of this effort indicated that while lifetime estimates may be above negligible, upper limits on short term risks are very low and should be considered irrelevant to this issue.

OPP is aware that older oncogenicity studies, upon initial or re-review may have been tested at doses lower than the predicted MTD. In the event that such testing appears to be at doses less than the predicted MTD, OPP has been reviewing and considering the entire

weight of the evidence to determine if retesting is necessary. Certain factors which affect the agency's decision to retest include but are not limited to the following: demonstrated oncogenicity in another species, nearness to the apparent MTD, genotoxic effects, structure-activity factors, absolute value of the highest dose tested and metabolic considerations.

HED has stated that our position, as to whether retesting was required in such instances, would be based upon all relevant information. In the current situation with fenoxaprop-ethyl, the weight of the evidence indicate that we consider the following:

a) there is an adequate chronic rat study

b) results of the mutagenicity assays were negative for each category of genotoxicity tested

c) available evidence does not indicate that fenoxaprop-ethyl is in a structural class to which known carcinogens belong

d) the available data provide a good margin of safety (i.e. calculations which compare the high dose in the mouse study to a human exposure level based upon 0.05 ppm in 100% of the diet; a very conservative approach).

However, it is HED's opinion, that the mouse study should be repeated based upon the MTD problem described above, namely, the HDT in the mouse cancer study (40 ppm) was only 1/8th of the dose (315 ppm) which resulted in kidney necrosis in females in the 32 day feeding study. This opinion is consistent with current MTD policy.

With these considerations in mind, fenoxaprop-ethyl is similar to our previous MTD decision for Rally[1] (short-term studies in both rats and mice indicated that in certain cases higher doses should have been tested). Therefore, based upon our re-review of the available information, in light of our current MTD policies, and the increased exposure, the mouse study should be repeated, although conditional registrations could be supported.

cc: A. Lindsay (H7505C)
S. Irene (H7505C)

1

[1] Note to Doug Campt from William Burnam, Attachment 3 - Summary of MTD decision on Nustar, Rally, and Londax.