MEMORANDUM

TO: Larry L. Nelson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
1020 N Street, Room 234
Sacramento, CA 95814

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental
Toxicology Section

DATE: April 1, 1994

SUBJECT: Draft Fenoxaprop-ethyl Risk Characterization

Thank you for the opportunity to review and comment on the draft risk characterization document for fenoxaprop-ethyl. Staff of the Pesticide and Environmental Toxicology Section have reviewed the document, however, we do not consider this review as complete because of the lack of data/information to support worker exposure calculations.

Our review is based on the assumption that the approaches and calculations used for exposure assessments are correct, but we would prefer reviewing a completed document at a later date.

The following underlines the most significant issues raised in our review. Detailed comments are provided in the attached memorandum.

Fenoxaprop-ethyl has not been registered in California. Before registration is granted, the Department of Pesticide Regulation (DPR) should make sure that all necessary environmental data are submitted in order to be prepared for any potential environmental disaster like the metam sodium spill. This especially applies to data on aquatic toxicity, since fenoxaprop-ethyl is extremely toxic to fish. We would appreciate being informed about the completeness of the environmental data for this chemical.

According to DPR, acute occupational exposure to fenoxaprop from aerial spraying may result in a margin of safety (MOS) below 100 (DPR's default value) for pilots (71) and flaggers (83). The same applies when seasonal exposure is considered for the pilots (MOS of 86). Adequacy of these MOSs for workers performing aerial spraying activities is even more questionable because of the severity of toxic effects (mortality) which served as a basis for the NOEL establishment. For such effects we recommend using a protective MOS higher than 100. (If using the reference exposure level or reference dose method, additional uncertainty factors would necessarily be applied because of the extreme nature of the endpoint).

DPR does not suggest any mitigation measures for the job activities with an inadequately health-protective MOS. Also there are no recommendations provided for the risk assessment managers and regulators as to the future actions that should be taken as a result of the risk appraisal performed. The next version of the document should be corrected by addressing these issues.

We thank you for sending us the document for review and alerting us in anticipation of the arrival of this document. However, we would still appreciate being able to perform our review in a less hurried fashion, especially when it applies to the registration of new active ingredients. It would improve both the risk assessment documents and the interactive process.

If you have any questions regarding our review or would like further discussions, please call me or Dr. Michael DiBartolomeis at (510) 540-3063.

cc: Jolanta Bankowska, Ph.D.
Rajpal Tomar, Ph.D.
Michael J. Dibartolomeis, Ph.D.
Robert A. Howd, Ph.D.

ATTACHMENT
REVIEW OF THE RISK CHARACTERIZATION DOCUMENT FOR FENOXAPROP-ETHYL

This report consists of three parts: background information, comments, and summary of conclusions and recommendations. The background information provides a brief summary of the characteristic features of fenoxaprop-ethyl and the Department of Pesticide Regulation's (DPR) risk characterization document for this chemical. Staff of the Pesticide and Environmental Toxicology Section reviewed the document and do not consider this review as complete because of the lack of data/information to support worker exposure calculations. We request the additional data for a full review in the next draft.

BACKGROUND INFORMATION

Use

Fenoxaprop-ethyl is a selective post-emergence herbicide which is used against perennial and annual grass weeds in many crops. Fenoxaprop-ethyl has not been registered in California. Currently the registrant is requesting a new Section 3 registration for use on rice in California, and this is the reason for performing the risk assessment for this chemical. Fenoxaprop-ethyl is formulated as an emulsifiable concentrate Whip 1EC which contains 12.5% of the active ingredient (1 pound per gallon).

Mechanism of action

Fenoxaprop-ethyl belongs to the aryloxy phenoxy-propionate class of herbicides. Other members of this group include: diclofop-methyl, fluazifop-butyl, and haloxyfop-methyl. These chemicals were found to interfere with normal lipid metabolism in sensitive plant and animal species. In their free acid form they inhibit *de novo* biosynthesis of fatty acids. The target enzyme for all four compounds was acetyl-CoA-carboxylase, the rate limiting enzyme in fatty acid biosynthesis. This enzyme is found in plants and also in mammals, in liver and adipose tissues.

Toxicology

DPR concluded that the main toxicological effects of fenoxaprop-ethyl result from hepatotoxicity. The majority of the effects observed are probably the consequence of inhibition of fatty acid biosynthesis in the liver. The most pronounced effects noted in acute, subchronic and chronic toxicity studies were liver changes. In the acute and subchronic toxicity studies liver weight increased, and in chronic toxicity studies the weight decreased. These effects are not necessarily adverse unless accompanied by other changes. Changes in liver weight were usually reversible-- in subchronic studies after the discontinuation of the exposure, and in chronic studies as a result of adaptation. In some studies, however, changes in liver weights were accompanied by fatty degeneration of the liver, enlarged centrilobular hepatocytes, and changes in liver enzymes.

Toxic effects caused by fenoxaprop-ethyl are not limited to the liver. The studies revealed that these effects often involve weight and histopathological changes in other organs such as the kidneys, lungs, thyroid, thymus, spleen and lymph nodes. Also, fenoxaprop-ethyl was found to produce an increased level of fetal anomalies (structural and visceral changes) in rats and rabbits, as well as maternal mortality in Cynomolgus monkeys.

The risk characterization document concludes that available data do not indicate any evidence of adverse effects on reproduction, oncogenicity, or genotoxicity.

Risk Appraisal

The health risks from exposure to fenoxaprop-ethyl were assessed for occupational (aerial and ground application) and dietary exposures. Occupational exposures were determined for pilots, mixer-loaders, flaggers, and ground applicators. Dietary exposure analyses were performed for the general population and for 22 population subgroups by using TAS computer programs for the acute and chronic conditions of exposure. Occupational exposures were assessed only for workers under acute and seasonal conditions of exposure.

Assessment of the health risk resulting from the acute and seasonal occupational exposures as well as from the acute dietary exposure was based on a NOEL of 10 mg/kg established in developmental toxicity studies. This NOEL was determined for increased skeletal and visceral fetal anomalies (mouse), and for maternal mortality (monkey). Assessment of the chronic dietary exposure was based on the U.S. EPA reference dose (RfD) of 0.0025 mg/kg-day. This RfD was based on a NOEL of 0.25 mg/kg-day determined for the decreased total blood lipids and cholesterol in the F1 generation in a rat reproductive study.

Margins of safety (MOSs) below 100 were found at the 95th percentile of occupational acute exposure for pilots (71) and flaggers (83). Also, based on mean estimated seasonal exposure, the MOS for pilots (86) was also below 100. The MOSs from dietary exposure to fenoxaprop-ethyl determined for the general population and 22 population subgroups were much greater than 100. Margins of safety below DPR's default value of 100 are usually considered inadequate and require mitigation to increase the safety margin.

Tolerances

Both acute and chronic dietary exposure analyses performed at the tolerance level showed that MOSs for consumers of commodities treated with fenoxaprop-ethyl were adequately health protective.

COMMENTS

Protectiveness of MOS

"A margin of safety (MOS) of at least 100 is generally recognized as protective of public health when the NOEL is based on toxicology data from animal studies," states the fenoxaprop-

ethyl risk characterization document. "At least" means that under certain justifiable circumstances a higher value should be used. Conditions when a higher value for a MOS (additional uncertainty factors applied to the NOEL) is commonly used include but are not limited to: the use of a LOEL (in the absence of the NOEL) value for risk assessment, extensive gaps in the toxicological data base, and severity of toxic effects produced by a subject chemical. This approach is commonly used by the U.S. EPA in establishing RfDs and drinking water standards (MCLs) and by OEHHA when performing risk assessments for the protection of the public and worker health.

The developmental toxicity study chosen by DPR for the acute risk assessment is an appropriate example of a situation where an additional uncertainty factor should be applied to the NOEL value to determine an adequately protective MOS. In this study conducted in Cynomolgus monkeys, a NOEL of 10 mg/kg-day was established on the basis of maternal mortality. DPR did not use any additional uncertainty factor that would account for the severity of this effect, but such a use is highly recommended under the circumstances. If an additional uncertainty factor was used, the safety margins noted elsewhere might be inadequate and cause for denial of registration.

Risk Appraisal and Conclusions

The Fenoxaprop-ethyl risk characterization document lacks suggestions for mitigation means for job activities with MOSs too low for acute and seasonal occupational exposure to this chemical. Also, the protectiveness of the MOS value of 100 is questionable (see above). In addition, the document lacks a section on recommendations for the risk managers and regulators as to the future actions that should be taken as a result of the appraisal performed. (Note: if this is to be included in a separate document we request a chance to review and offer comments on this).

Potential for Immunotoxicity

In a few animal studies described in the risk characterization document, fenoxaprop-ethyl caused adverse effects which might indicate its potential for immunotoxicity. These effects include: atrophy of the splenic capsule and thymus, atrophy of the thymus and hyperplasia of the lymph follicles observed in a 30-day dietary study in dogs, and a decrease in absolute thymus weight in offspring and in spleen weight in females in a reproductive toxicity study in rats.

There is currently no requirement for testing or evaluating the chemical's potential for immunotoxic effects. However, the signs of possible immunotoxic effects should not be disregarded and the issue should be addressed as a part of the risk characterization, albeit qualitatively if necessary.

Worker Exposure

Absorbed daily dosage (ADD) and seasonal average daily dosage (SADD) were estimated for aerial application using a surrogate study of worker exposure to the herbicide Londax. For ground application, a surrogate study used a Whip occupational exposure study on soybeans.

There is no substantiation provided in the document for the choice of Londax as an appropriate surrogate for estimating exposure to fenoxaprop-ethyl. Also there are no details given on how to calculate exposures for different job activities under different scenarios. Usually risk assessment documents contain an appendix on worker exposure assessments where the relevant exposure studies and details on calculations are provided. This document does not provide data (either within the text of the document or in a separate appendix) to support values presented in the section on exposure assessment.

The document does not provide any values for the annual absorbed daily dosage (AADD) and the lifetime absorbed daily dosage (LADD). DPR believes that it is "inappropriate" to calculate these exposures because of "the strictly seasonal use of Whip on rice, the reversal of sub-chronic toxicity following a recovery period and the lack of oncogenicity in the long-term studies". We do not think these arguments are not sufficient to justify "inappropriateness" of calculations of the AADD and LADD.

Among the subchronic studies (in rats, mice and dogs) presented under Toxicology Profile (pg.13-16), reversibility of toxic effects was observed only in rat studies. In the mouse study, hepatotoxic effects were described as "dose-dependent changes in hepatic epithelia with large nuclei and dense eosinophilic cytoplasm in the centrilobular region of the liver". The document states that "Reversibility was not noted in this study". In the description of the dog study there is no information provided on reversibility of the toxic effects. Also there is no information within the body of the document that would indicate that the rat is a better model for human toxicological responses to fenoxaprop-ethyl than the mouse.

Furthermore, animal subchronic studies do not adequately reflect worker conditions of exposure. Workers incur repeated seasonal (occupational) exposures which may be accompanied by chronic (dietary) exposure to fenoxaprop-ethyl. Reversibility of the toxic effects caused by fenoxaprop-ethyl under these conditions may be compromised. Moreover, it can not be excluded that potential worker exposure to other chemicals, especially to the herbicides of the same mechanism of action (aryloxy phenoxy-propionates), would not further increase the risk of the irreversibility of hepatotoxic action of fenoxaprop-ethyl. Chronic exposures must be calculated to allow estimation of combined exposures to multiple residues.

Multiple Exposure to Other Hepatotoxic Herbicides

We are concerned that the health risk for hepatotoxic effects as a result of the inhibition of fatty acid biosynthesis in the liver may not be limited to exposure to fenoxaprop-ethyl. If there is a potential for exposure to other pesticides with the same mechanism of action, then a health risk assessment should be performed for the combined exposure to all relevant chemicals. We would appreciate being informed about the registration status or future plans for registration in California of the aryloxy phenoxy-propionate class of herbicides (diclofop-methyl, fluazifop-butyl, and haloxyfop-methyl), and whether the seasonal exposures of the workers applying this pesticide would be likely to be followed by exposures to the other herbicides during a normal season.

Omissions and Lack of Clarity

There is no information provided within the document on the potential of fenoxaprop-ethyl to cause skin sensitization; this should be discussed. Information on the U.S. EPA reasoning for using an abnormal blood lipid level as a basis for RfD establishment should be further discussed since DPR questions the toxicological relevance of this end point (pg. 28). A definition of the term "definitive study" (used in different places under "Toxicology Profile") should be provided. Also, the use of cryptic abbreviations should be proceeded by a full description of the term, e.g., preharvest interval for PHI. Description of the reproductive toxicity study (pg. 21) should be more specific. It is not clear if the effects produced in offspring refer to all generations of the offspring or to a specific generation.

SUMMARY OF COMMENTS AND RECOMMENDATIONS

General comments

1. We request that DPR inform the Office of Environmental Health Hazard Assessment (OEHHA) about the completeness of the data base (including environmental and residue data) necessary for registration of a new chemical in California.

2. We also request that OEHHA be informed about current or pending uses of other aryloxy phenoxy-propionate herbicides in California.

Recommendations specific to the risk assessment document for fenoxaprop-ethyl

1. Complete the document by providing data on worker exposure assessment.

2. Substantiate the use of Londax as an appropriate surrogate chemical for assessing exposure to fenoxaprop-ethyl.

3. Use an additional uncertainty factor(s) to increase the margin of safety to account for the severity of toxic effects (maternal mortality in monkeys) produced in the developmental toxicity study and used as a basis for calculating health risk from the acute and seasonal exposure to fenoxaprop-ethyl.

4. Address the potential for immunotoxic effects from exposure to fenoxaprop-ethyl.

5. Provide information on skin sensitization.

6. Address the issue of multiple exposure to other herbicides with the same mechanism of action as fenoxaprop-ethyl.

7. Discuss available mitigation measures in order to increase the MOS level for job activities with inadequate health protection.

8. Provide clear recommendations for the risk managers and regulators as to further actions on registration of fenoxaprop-ethyl in California (or submit a separate document outlining these recommendations).