UNITED S TES ENVIRONMENTAL PROTECTIO. AGENCY 188AAA

DATE: December 1, 1978

SUBJECT: Issues relating to the mouse oncogenicity studies for Dichlofop (Hoechst) and Goal (Rohm & Haas).

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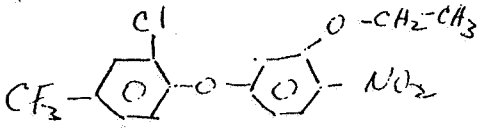
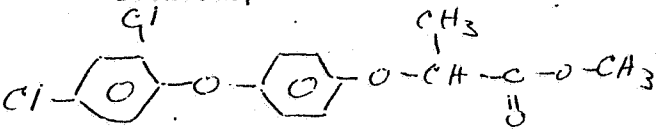
1. Both chemicals are relatively new herbicides belonging to the same chemical class.

Goal



Dichlofop



2. The Goal 20 month mouse study was originally reviewed about a year ago. The Dichlofop 2 year mouse study was reviewed in the last few weeks.

In the Dichlofop 2 year mouse study, the presence of liver cell nodules in mouse livers of the high-dose mice was listed by the registrant as tumors (see attachments) and in the narrative, by the pathologist, described as benign hepatomas and, in part, as their pre or early stages. The pathologist later states that predominantly regenerative hyperplastic processes are responsible for the increase of liver cell nodules rather than primarily carcinogenic effects.

In the 20 month mouse study with Goal the pathologist (Dr. Newberne) stated that there was no increase in neoplasms in the high-dose group and that the hyperplastic nodules were regenerative and compensatory effects of liver damage.

3. During the regular review of the Dichlofop data there was mounting pressure for a Section 18 evaluation. Because a decision was needed as soon as possible Mr. Rhodier (Special Registration Section) suggested the help of an in-house oncologist (Dr. Diane Beal). Dr. Beal stated that the nodules represent tumor formation (see attachment). The interpretation of the liver effects as tumors was the basis for considering that an oncogenic RPAR criterion may have been exceeded.

The final review of the Dichlofop petition PP# 8F2110 was sent to Chief Toxicology Branch for further consideration re. referral to RPAR or other action.

4. There was a pending action on Goal as well, PP# 8G2028. In light of the experience with Dichlofop the Goal mouse study was again looked at critically, since hyperplastic liver nodules were reported in that study as well.

5. It now appeared that the two chemicals may have the same or similar effects on mouse livers. This conclusion is also supported by the structural similarity of the two compounds. Rohm & Haas was thus informed about our uncertainty about the "liver nodules" produced by their compound.

6. On a recent visit to Germany I had the occasion to meet Dr. Kief, the pathologist responsible for the Dichlofop study. I discussed the problems in depth with him and the following picture emerged. Dr. Kief is of the opinion that mouse "liver nodules" can not be differentiated with the same ease as rat liver nodules, thus he classified them simply as "liver nodules". They are of no different morphological quality then the spontaneous nodules in untreated mice, only their number is increased in the 20 ppm mice. A number of other factors, environmental (overfeeding, starvation) or pharmacologically active substances (hormones, lipid reducers) have the same effect. Since Dichlofop is reducing blood lipid levels, the liver nodule formation was expected and is considered a pharmacologically based response. This explanation and argument, to my knowledge, was not contained in the petition, nor were pharmacological studies showing the lipid reducing effect.

7. Present Status:

A. Goal - The pathologist Dr. Newberne was consulted at a recent meeting (November 22, 1978). Toxicology Branch accepted and agreed with Dr. Newbernes opinion that the hyperplastic nodules are a result of focal necrosis followed by tissue regeneration. An oncogenic risk criterion has not been triggered.

B. Dichlofop

a. The Section 18 risk assessment is not complete, however, it progresses in the direction of an oncogenic risk assessment (Memo Dr. Mishra, November 20, 1978).

b. The final review is still under consideration by Chief Toxicology Branch. No decision whether to forward to RPAR or not has been made, to my knowledge.

8. Future Course:

It still appears that the two chemicals show the same pharmacological-toxicological picture. They produce liver nodules; toxicologically induced (necrosis) or possible pharmacologically induced (lipid reduction-necrosis). Yet the two actions described under #7 above are taking a quite different course.

Since an ad hoc decision was reached on Goal an ad hoc decision on Dichlofop should be reached as well by consultation with pathologists and an official deliberation by the Company along the lines of the personal discussions held.

The issue however goes beyond these two chemicals and becomes a basic question: Is an increase of "liver nodules" in mice as a result of regenerative repair of necrosis, an indication of oncogenesis/oncogenesis promotion or not?

Since this is a highly controvercial question and the problem will recur as more chemicals are tested in mice, an ad hoc resolution in each case does not seen to be advisable, a general policy should be established instead. The inconsistency in resolving the "liver nodule" problem on an ad hoc basis is well illustrated on the example of Goal and Dichlofop. The inconsistency was precipitated simply by diverging terminologies of two pathologists, whereas their scientific opinion actually was the same. The SAP or SAB may be the adequate forum for deliberating the question. The desperate need for a pathologist serving the Toxicology Branch is also obvious from the above discussion.

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cc: Dr. Dykstra

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