



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

APR 28 1987

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 100-541. Atrazine and Simazine.
Protocols for Conducting Animal Metabolism Studies.
RCB No.: 2107. MRID/Access. No.: None.

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Ciba-Geigy Corporation has submitted two protocols for animal metabolism studies (lactating goat; chickens) for comment by RCB.

Both these studies will entail dosing with ¹⁴C-G-28273, the didealkylated chlorotriazine plant metabolite of atrazine and simazine.

The petitioner states animal metabolism studies (lactating goat; chickens) with atrazine and simazine (fed separately; no protocols submitted) will be conducted as well.

The petitioner proposes not to conduct animal metabolism studies (lactating goat; chickens) with the monodealkylated chlorotriazine products, G-30033 and G-28279.

The petitioner also proposes not to conduct ruminant or poultry feeding studies with the chlorotriazine metabolites.

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Background

Atrazine and simazine have been the subjects of Registration Standards.

The guidance documents for the reregistration of pesticide products containing atrazine (issued 9/85) or simazine (issued 3/84) as the active ingredient identify data gaps under 40 CFR 158.125 pertaining to animal metabolism and feeding.

Those data gaps, as discussed in the science support chapters produced by RCB on atrazine (dated 7/83) and simazine (dated 8/83), are restated below.

Atrazine 171-4: Nature of the Residue (Metabolism) - Animals

"Studies are required which elucidate the metabolism, distribution, and accumulation of [¹⁴C]atrazine in poultry and ruminants, including eggs and milk, respectively."

171-4: Magnitude of the Residue - Meat, Milk, Poultry, and Eggs.

"Residue data for eggs and the fat, meat, and meat by-products of poultry reflecting hen feeding studies at 0.2, 0.6, and 2 ppm (1X, 3X, and 10X the highest expected dietary intake of atrazine by poultry)" are required.

"If additional metabolites of concern are indicated [in the ruminant metabolism study requested], then additional feeding studies with ruminants may be required."

"If the metabolism study with poultry does not detect additional metabolites of concern besides atrazine per se in poultry meat and eggs then the requested feeding study with poultry may be waived."

Simazine 171-4: Nature of the Residue (Metabolism) - Animals

"Studies which elucidate the metabolism of simazine and its chlorometabolites G-28273 and G-28279 in poultry (including eggs) and ruminants (including milk) are required; if

the metabolism of simazine and its chloro-metabolites in poultry or ruminants is found to differ significantly from that in rats, a non-ruminant (swine) study will also be required."

"Identification and quantification of simazine and possible metabolites of toxic concern in tissues of various organs (muscle, heart, liver, kidney) and milk is essential. The results of this metabolism study will determine whether or not additional feeding studies are needed.

171-4: Magnitude of the Residue - Meat, Milk, Poultry, and Eggs.

"A feeding study with poultry which are fed simazine per se and its two chlorometabolites [G-28273 and G-28279] individually at levels of 1X, 3X, and 10X the highest expected dietary intake by poultry [is required]. (Appropriate dosage levels for feeding of metabolites cannot be determined until sufficient metabolite residue data for feed items have been received.) In this study tissues and eggs must be analyzed for simazine per se, its two chloro-plant-metabolites and any significant animal metabolites found in the poultry metabolism study requested under 'Nature of the Residues in Animals'."

"Depending upon the results of the requested animal metabolism study with ruminants, a feeding study with ruminants may be needed where animals are fed the two chlorometabolites [G-28273 and G-28279] individually at levels of 1X, 3X, and 10X the highest expected dietary intake by ruminants. In this feeding study residue levels of simazine plant and animal metabolites of toxicological concern (if present as determined by the ruminant metabolism study) must be determined in the milk, fat, meat, and meat byproducts of ruminants."

Discussion

Subsequent to the development of these Registration Standard documents on atrazine and simazine, RCB issued a memorandum, "Material [to be] Fed in Animal Metabolism Studies", 4/16/85, C. L. Trichilo, which clarified our Guideline requirements [Pesticide Assessment Guidelines, Subdivision O - Residue Chemistry] in the area of livestock metabolism studies.

That memorandum states that "animal metabolism studies should reflect feeding of one compound, usually the parent." If "plant metabolites are also found to be animal metabolites, then additional metabolism studies involving dosing with the metabolites will not generally be required."

For now, it would thus be sufficient for Ciba-Geigy to conduct animal metabolism studies (lactating goat; chickens) for the parent compounds, atrazine and simazine, only.

If chlorotriazine plant metabolites are demonstrated by these new metabolism studies to be animal metabolites as well, then additional animal metabolism studies (lactating goat; chickens) in which individual chlorotriazine plant metabolite(s) are fed will not be required.

If, however, chlorotriazine plant metabolites are not found as animal metabolites, then additional animal metabolism studies (lactating goat; chickens) will be required in which the chlorotriazine plant metabolite(s) are fed individually, based on the composition of the terminal residue in plants.

If Ciba-Geigy elects to conduct animal metabolism studies (lactating goat; chickens) with the chlorotriazine plant metabolite G-28273 at this time, we do not object.

However, Ciba-Geigy should be advised that such studies with chlorotriazine plant metabolites may not be required at all (i.e., if the chlorotriazine plant metabolites are found to be animal metabolites as well).

Conversely, Ciba-Geigy should also be informed the results of the ruminant and poultry metabolism studies with atrazine and simazine per se may engender the need for animal metabolism studies with chlorotriazine plant metabolites other than just G-28273 (each to be fed individually), depending on the composition of the terminal residue in plants.

It is essential the animal metabolism studies be conducted in such a manner that identification and quantification of the residue in tissues, organs, milk, and eggs are possible. We therefore caution Ciba-Geigy to select sufficiently high dosing levels, specific activity material, and numbers of test animals to ensure this.

In examining the two protocols which Ciba-Geigy has submitted for RCB comment, we are concerned as to whether a 5 ppm dosing level is sufficiently high for this purpose, and whether use of only 2 test chickens will provide enough sample.

Poultry feeding studies with parent atrazine and simazine are required. The results of the animal metabolism studies (lactating goat; ruminant) with atrazine and simazine per se will determine whether or not ruminant and poultry feeding studies with their chlorotriazine plant metabolites are also required. RCB defers judgment on this issue pending the results of the animal metabolism studies with atrazine and simazine.

Conclusions

1. Ruminant and poultry metabolism studies with only atrazine and simazine per se need be initiated now.
2. Whether ruminant and poultry metabolism studies with chlorotriazine plant metabolites of atrazine and simazine need be run will depend upon the findings of the animal metabolism studies with atrazine and simazine per se. (See Discussion section of this review.)
3. We would not object if ruminant and poultry metabolism studies were initiated at this time with G-28273.
4. It is possible that ruminant and poultry metabolism studies will be needed for chlorotriazine plant metabolites other than just G-28273. (Depending on the findings of the animal metabolism studies with atrazine and simazine per se; see Discussion section of this review.)
5. It is essential the animal metabolism studies be conducted in such a manner that identification and quantification of the residue in tissues, organs, milk, and eggs are possible.

We caution Ciba-Geigy to utilize sufficiently high dosing levels, specific activity compounds, and numbers of test animals to ensure this.

We are concerned as to whether a 5 ppm dosing level is sufficiently high for this purpose, and whether use of only 2 test chickens will provide enough sample.

6. Poultry feeding studies with parent atrazine and simazine are required.

7. The results of animal metabolism studies (lactating goat; ruminant) with atrazine and simazine per se will determine whether or not ruminant and poultry feeding studies with their chlorotriazine plant metabolites are also required.

RCB defers judgment on this issue pending the results of the animal metabolism studies with atrazine and simazine per se.

Recommendations

We recommend that Ciba-Geigy be informed of the Conclusions drawn in this review.

We further recommend that a copy of this full review be sent to Ciba-Geigy.

cc: RF, Circ, Reviewer (Nelson), TOX, EEB, EAB, PM#23, Atrazine Registration Standard File, Simazine Registration Standard File, ISB/PMSD (Eldridge).

TS-769C:RCB:Reviewer(MJN):CM#2:Rm804:557-7484:typist(mjn):4/23/87.

RDI:SectionHead:RSQuick:4/23/87:DeputyChief:RDSchmitt:4/24/87.