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

MAR 10 1993

MEMORANDUM:

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Chlorpropham. Reregistration Case No. 0271. Issues to be presented at the 3/16/93 meeting of the HED Metabolism Committee.

FROM: John Abbotts, Chemist
Special Review Section II
Chemistry Branch II - Reregistration Support
Health Effects Division [H7509C]

THRU: Francis B. Suhre, Section Head
Special Review Section II
Chemistry Branch II - Reregistration Support
Health Effects Division [H7509C]

TO: HED Metabolism Committee [H7509C]

Summary

Tolerances for chlorpropham are presently expressed as residues of parent and one metabolite. Registrant has voluntarily cancelled all uses except post-harvest treatment of potatoes. For this use, parent represents 96% of total residues, and no single metabolite represents more than 1.25% of total residues. The Committee is requested to determine if it would be appropriate to change the tolerance expression to regulate residues of parent alone. A related matter is whether concentration of parent and 3-chloroaniline residues during potato processing is of concern.

Residue Chemistry in Plants

Tolerances are established for residues of the plant regulator and herbicide chlorpropham, isopropyl 3-chlorocarbanilate (CIPC), and its metabolite 1-hydroxy-2-propyl-3'-chlorocarbanilate (isopropyl-OH-CIPC), in or on potatoes and soybeans (40 CFR 180.181). Interim tolerances are established for residues of chlorpropham on numerous plant and animal commodities, pending establishment of permanent tolerances (40 CFR 180.319).

The Residue Chemistry Chapter (8/14/87) concluded that the nature of the residue in field-treated, growing crops was adequately understood. The major residues identified in growing plants were chlorpropham, isopropyl-OH-CIPC (IV), 2-OH-CIPC, 4-OH-CIPC, and

6-OH-CIPC; residues of 3-chloroaniline (VI) were also detected in several crop species. The Guidance Document (12/87) required additional metabolism data on residues in potatoes treated post-harvest with chlorpropham. The Guidance Document also required data on residues of 3-chloroaniline, identified as a probable mutagen.

In response to the Guidance Document, registrants indicated the intent to voluntarily cancel all outdoor uses of chlorpropham on food and feed commodities. Residue chemistry data consistent with continued registration for post-harvest treatment on potatoes were still required. Registrant has submitted an acceptable metabolism study, and the nature of the residue in potatoes treated post-harvest is adequately understood (CBRS 8942ff, 3/xx/93, J. Abbotts). Potatoes were treated at 2.4X the maximum label rate, and stored for 52 weeks post-treatment.

Residues identified are indicated in Table 1, and structures are shown in Table 2 (for simplicity, only the structures of detected metabolites are shown). Parent chlorpropham represented 96% of the total radioactive residue (TRR); metabolites were identified, but each represented no more than 1.25% TRR. Metabolite IV, included in the present tolerance expression, was not identified, but an oligosaccharide conjugate (XX), represented 0.03% TRR. 3-chloroaniline and its glucose conjugate were identified, at a combined level of 0.58% TRR. Parent chlorpropham was thus present at levels two orders of magnitude greater than combined 3-chloraniline residues, and at levels three orders of magnitude greater than the isopropyl-hydroxy conjugate. It is of interest to determine if the tolerance for post-harvest treatment of potatoes can be expressed as residues of parent only.

It should be noted that the Residue Chemistry Chapter (8/14/87) reported that levels of metabolite IV in growing plants represented up to 20% of TRR.

<u>Potato Residue Chemistry Data</u>

Residue chemistry data have been provided for potatoes and potato processed commodities (CBRS No. 11008). This study has not yet been reviewed, but the data provided by registrant can be reported. Residues of chlorpropham and 3-chloroaniline were measured on potatoes treated post-harvest by fogger at 1 lb ai per 60,000 lb potatoes, and on processed commodities. Residues on peel at 2 hr following treatment were a maximum of 10.7 ppm chlorpropham and 0.39 ppm 3-chloroaniline. Residues declined modestly with time, and at 106 days following treatment residues on peel were a maximum of 8.7 ppm chlorpropham and 0.08 ppm 3-chloroaniline. Residues of chlorpropham did not concentrate in potato chips or granules during processing; residues of 3-chloroaniline did not concentrate in granules, but did concentrate in potato chips by up to 2-fold (91.2 ppb in chips v.

45.8 ppb in whole potatoes). Residues of both compounds concentrated in dried peels, chlorpropham by up to 12.4-fold (75.6 ppm in dried peels v. 6.11 ppm in whole potatoes) and 3-chloroaniline by up to 13.4-fold (614 ppb in dried peels v. 45.8 ppb in whole potatoes). Registrant noted that the laboratory procedure to dry the skins did not simulate the commercial method of dried skin preparation, but did not provide data that would be consistent with commercial procedures.

The data provided are sufficient to indicate that residues of chlorpropham concentrate in dried peels during processing, and residues of 3-chloroaniline concentrate in potato chips and dried peels during processing. It would be of interest to know if concentration of chlorpropham and/or 3-chloroaniline during processing is of toxicological concern.

Analytical Methods

The Residue Chemistry Chapter (8/14/87) concluded that data collection and enforcement methodology should include pre-hydrolysis and hydrolysis extraction steps in order to detect free and conjugated side-chain modified metabolites, such as isopropyl-OH-CIPC and 3-chloroaniline. The Guidance Document (12/87) specified that methods used for data collection and tolerance enforcement, including methods for 3-chloroaniline, be tested with regard to their efficiency in extracting bound residues, using radiolabeled samples from metabolism studies. The Update to the Residue Chemistry Chapter (10/16/91) reiterated these requirements and added that proposed enforcement methodology should be validated by an independent laboratory prior to submission for Agency validation.

Registrants submitted data on an analytical method for potatoes which detected parent and metabolites p-hydroxychlorpropham (III), p-methoxychlorpropham (X), and 3-chloraniline (VI). Residues were extracted from potatoes and analyzed by GLC with nitrogen-phosphorus detection (NPD); compounds are identified as separate peaks. Recoveries of parent and the first two metabolites from fortified potato samples were adequate; however, recoveries of 3-chloroaniline averaged 40% and were inadequate. The review noted that a new method would be required if 3-chloroaniline or other metabolites were designated residues to be regulated (CBRS 8942ff, 3/xx/93, J. Abbotts). Additional data required for an enforcement method, including radio-validation with metabolism samples and independent validation by a second laboratory, remain outstanding.

Questions for the Metabolism Committee

1. Are the levels of metabolites in potatoes treated post-harvest of sufficient toxicological concern that they should be included in the tolerance expression, or can the tolerance be expressed as residues of parent alone?

2. Is the concentration of chlorpropham and 3-chloroaniline residues during potato processing a matter of toxicological concern?

cc:Circ, Abbotts, RF, Reg. Std. File, SF
RDI:FBSuhre:3/9/93:MSMetzger:3/9/93:EZager:3/10/93
H7509C:CBII-RS:JAbbotts:CM-2:Rm805A:305-6230:3/10/93

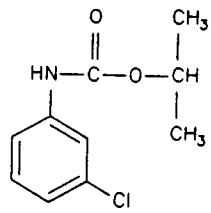
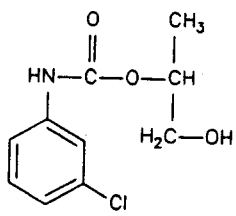
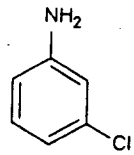
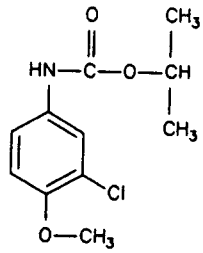
Table 1. Identification and characterization of radioactive residues in or on potatoes treated postharvest with [^{14}C]chlorpropham and stored at 8°C for 52 weeks.

Metabolite[1]	Pulp		Peel		Methanol Wash		Total	
	%TRR	PPM[2]	%TRR	PPM	%TRR	PPM	%TRR	PPM
chlorpropham	1.21	0.351	8.26	2.396	86.44	25.075	95.91	27.822
p-methoxychlorpropham (X)	0.05	0.015	-	-	-	-	0.05	0.015
3-chloroaniline (VI)	-	-	0.35	0.102	-	-	0.35	0.102
3-chloroaniline-N-glucosylamine (XIX)	0.18	0.052	0.05	0.015	-	-	0.23	0.067
4-hydroxychlorpropham oligosaccharide conjugate (XXI)	0.51	0.148	0.74	0.215	-	-	1.25	0.363
1-hydroxychlorpropham oligosaccharide conjugate (XX)	-	-	0.03	0.009	-	-	0.03	0.009
4-hydroxychlorpropham amino acid conjugate (XXII)	0.51	0.148	0.06	0.017	-	-	0.57	0.165
Unknowns								
Polar unidentified	0.15	0.044	0.12	0.035	-	-	0.27	0.079
Hexane soluble	0.05	0.015	-	-	-	-	0.05	0.015
Enzyme-hydrolyzed aqueous	0.04	0.012	0.17	0.049	-	-	0.21	0.061
Unextracted residues	0.19	0.055	-	-	-	-	0.19	0.055
Total	2.89	0.838	9.78	2.838	86.44	25.075	99.11	28.751

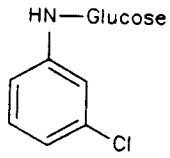
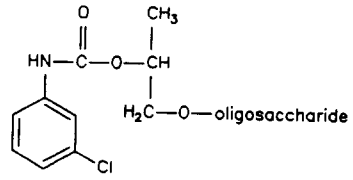
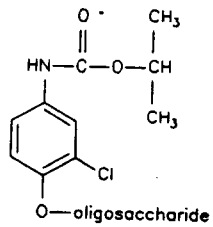
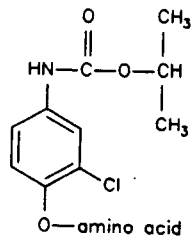
1. See Table 2 for structures of metabolites.

2. The ppm is expressed on the basis of weight of pulp or peel.

Table 2. Metabolites of chlorpropham in potatoes treated post-harvest.

Code Number	Chemical Names (Common names)	Chemical Structure	Substrate; MRID	
I	isopropyl 3-chlorocarbanilate isopropyl m-chlorocarbanilate (chlorpropham; CIPC)		soybean potato egg white yolk hen liver kidney skin fat	00035485 00114794 00035480 42085601 42130401 42130401
IV	1-hydroxy-2-propyl-3-chlorocarbanilate (40 CFR 180.181) (hydroxymethyl)ethyl-3-chlorocarbanilate 1-hydroxychlorpropham (isopropyl-OH-CIPC)		soybean orchard grass turnip egg white yolk	00035485 00114794 00035480 00036395 00036640 00036638 00036639 42130401
VI	3-chloroaniline (chloroaniline)		potato	42085601
X	*p*-methoxychlorpropham		goat kidney potato	42112201 42085601

(continued)

Code Number	Chemical Names (Common names)	Chemical Structure	Substrate; MRID
XIX	3-chloroaniline-N-glucosylamine		potato 42085601
XX	oligosaccharide conjugate of 1-OH-CIPC		potato 42085601
XXI	oligosaccharide conjugate of 4-OH-CIPC		potato 42085601
XXII	amino acid conjugate of 4-OH-CIPC		potato 42085601