Dow Chemical Company requests the establishment of tolerances for combined residues of the insecticide chlorpyrifos [0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl) phosphorothioate] and its metabolite 3,5,6-trichloro-2-pyridinol in or on the raw agricultural commodities.

R.A.C. Proposed Tolerances

Soybeans 1 ppm
Soybean forage 8 ppm
Soybean straw 15 ppm
Fat, meat, and meat by-products of goats and sheep 1 ppm

Established tolerances (40 CFR 180.342) range from 2 ppm in or on broccoli, cabbage and cauliflower to 0.05 ppm for a variety of commodities. Tolerances have also been established for the fat, meat, and meat by-products of cattle (1.5 ppm), goats, hogs, horses and sheep (0.1 ppm), turkeys (0.2 ppm) and other poultry (0.01 ppm); eggs (0.01 ppm); and milk fat (0.25 ppm, 0.01 ppm in whole milk). The petitioner is proposing to amend the tolerances for fat, meat and meat by-products of goats and sheep.

Tolerances have been recommended for nectarines, rutabaga roots, radishes, and cole crops. Tolerance proposals are still pending for a variety of crops as requested in PP# 6F1830, PP# 8Z2092, PP# 9F2193, PP# 9E2215, PP# 9G2168, FAP# 9H5204, PP# 9F2221, FAP# 9H5227 and PP# 0F 2281.

Conclusions

1. A minimum time period between applications of Lorsban 4E should be indicated on the label.

2a. Chlorpyrifos undergoes extensive metabolism in or on soybeans. A number of metabolites in the bean metabolism
study remain to be identified. Consequently, the plant metabolism of chlorpyrifos is not adequately delineated for the proposed use. Further identification of the residue in the available plant metabolism studies is needed. If any additional metabolites are judged in need of regulation, then appropriate processing studies and residue data determined by a validated analytical method (which may have to undergo a method trial) will be needed.

2b. The animal metabolism of chlorpyrifos is not adequately characterized. The petitioner should elucidate metabolism of radiolabeled chlorpyrifos in a lactating goat. Furthermore, should other metabolites require regulation as a result of the resolution of conclusion 2a, additional animal metabolism studies of these metabolites may be needed.

3. Adequate analytical methods are not available to enforce the proposed tolerance for residues of chlorpyrifos and TCP because the apparent residues on untreated samples are exceptionally high especially on the straw. The petitioner should either explain why certain controls are high or improve the methods (the improved method may have to undergo a method trial) or submit additional data.

3b. The method is adequate for obtaining residue data.

4a. The residue data is inadequate because of the small number of field studies for forage and straw (hay), lack of data reflecting aerial applications and broad range of residue levels. The petitioner is advised to collect additional residue data from the major soybean producing states reflecting the maximum proposed use and forage and straw, aerial applications (or delete this use from Section B), the granular formulation and all regulated residues including significant metabolites found in the plant metabolism studies. If and when the tolerances are proposed, the tolerance for straw should be expressed in terms of hay.

4b. The processing study involves the analysis of one soybean sample. The presence of low residues on soybeans and residues in or on meal equal to that of soybeans, gives us no assurance that meal residues would not exceed those in the bean and that a food additive tolerance is not needed for meal. The petitioner is advised to perform a processing study using soybeans fortified with the regulated components of the residue at the tolerance level. We will withhold judgement on whether a food additive tolerance is needed for
the other processed fractions until the plant metabolism
question is resolved.

5. Due to conclusions 2a, 2b, 4a and 4b, we cannot conclude
whether secondary residues in meat, milk, poultry and eggs
will exceed existing or proposed tolerances. We will
withhold a conclusion on the proposed increases in
tolerances for meat, fat and meat by-products of goats and
sheep until these deficiencies are resolved.

Recommendations

We recommend against the proposed tolerances for the reasons cited
in conclusions 1, 2a, 2b, 4a, 4b, and 5. A favorable recom-
mandation is contingent upon resolution of these deficiencies.

Detailed Considerations

Formulations

Lorsban 42® (EPA Registration No. 464-448) and Lorsban 15G®
(EPA Registration No. 464-523) a granular formulation, are
proposed for use and contain 40.7% chlorpyrifos (4 lb ai/gal) and
15% chlorpyrifos respectively. The inert ingredients,
are cleared for use under Sec. 180.1001(c).

The manufacturing process has been described in our review of PP
41455 (memo: A. Smith, 5/3/74). The impurities in the technical
material comprise 6%.

The remainder, the nonvolatiles (40.4% each), consists of at least
seven compounds. We do not expect the impurities in Lorsban to
present a residue problem due to the dilution rates upon
application.

Proposed Use

Lorsban 42 is to be used for control of the following pests at the
dosages indicated:

Lesser cornstalk borer, 2 lb ai/A at planting or post-emergence
in a 6 to 10-inch-wide band followed by light incorporation; 1 lb.
ai/A at cracking in a 6 to 10-inch wide band followed by a second
spray 5 days after the initial treatment.
Cutworms, European corn borer, corn earworm, southern green stink bug, bean leaf beetle, Mexican bean beetle, armyworms, velvetbean caterpillar and green cloverworm at rates up to 1 lb ai/acre as a broadcast, foliar spray using ground or aerial equipment when field counts indicate damaging insect populations are developing or present; re-treat if necessary.

Restrictions are: do not apply more than 5 lb ai/acre per season, do not apply within 28 days before harvest, do not allow livestock to graze in treated areas nor otherwise feed treated soybean forage to meat or dairy animals within 14 days after application, and do not feed straw from treated soybeans to meat or dairy animals within 28 days after application.

Lorsban 15G, for control of the larvae of the lesser cornstalk borer is to be applied at planting time or post-emergence as a band (row) treatment at the rate of 1.2 oz ai/1000 ft of row (1.8 lb ai/acre for 21-inch row space or 1 lb ai/acre for 40 in. row space), and incorporated into the top 1 inch of soil by placing in a 6 to 7-inch-wide band. The label carries the restriction: do not make more than one application per season.

A minimum time period between applications of Lorsban 4E should be indicated on the label.

Nature of Residue

Plant

No metabolism data was submitted with this petition. The information is available in PP# 3F1306 and last discussed in our review of PP# 9F2221 (memo: E.M.K. Leovey, 2/8/80).

Briefly, the metabolism of both $^{36}$Cl and $^{14}$C-chlorpyrifos has been observed in bean and corn plants. Chlorpyrifos is translocated to only a limited extent from the surface of leaves and from soil. Chlorpyrifos undergoes degradation in ultraviolet light readily in the presence of water by dechlorination to the formation of diols and triols which can undergo ring cleavage. Under prolonged irradiation, the products were apparently carbon dioxide, ammonium carbonate and sodium chloride. The activity translocated after application to leaves could partially be ultraviolet decomposition products.

Actual plant metabolism is via hydrolysis to ethyl 3,5,6-trichloro-2-pyridyl phosphate; 3,5,6-trichloro-2-pyridyl phosphate; 3,5,6-trichloro-2-pyridinol (TCP); and material postulated to be a TCP
conjugate which comprises 4-29% of the translocated material. TCP can undergo dechlorination and formation (as observed in UV degradation) of diols and triols which can be conjugated or incorporated into natural plant constituents.

In soil, chlorpyrifos is slowly hydrolyzed to TCP. The extent to which TCP is translocated is dependent on pH. Above pH 7, the salt form predominates and, due to its water solubility, is readily translocated. The majority of the material translocated from the soil to plants was unidentified but considered to be derived from TCP. The existence of a conjugate was ruled out in corn since TCP residues were not increased by enzymatic hydrolysis.

Based upon the residue data, residues of TCP could be greater than or equal to residues of the parent. This would indicate that chlorpyrifos undergoes extensive metabolism in or on soybeans. Since a number of the metabolites in the bean metabolism study remain to be elucidated and residues of chlorpyrifos and TCP are significant, we conclude that the nature of the residue is not adequately delineated for the proposed use. (This question did not arise in connection with earlier uses on field crops because those uses were either at planting or were seed treatments.)

The petitioner should identify the uncharacterized TLC spots in the plant metabolism studies.

Animal

Metabolism in animals has been described in our review of PP# 3F1306 (memo F.D.R. Gee, 3/1/73). In rats, $^{14}$C and $^{36}$Cl chlorpyrifos and $^{14}$C-TCP were extensively eliminated in the urine and feces. Only 1.1-2.5% of the dose remained in tissues with residues highest in liver, kidney, stomach and blood.

Five ppm (cold) chlorpyrifos was fed to a lactating cow for four days. After methylation, urinary metabolites were identified (based upon GLC retention times) as the methyl esters of diethylthiophosphate and diethyl phosphate which were 35.9 and 26.8% of the insecticide fed. No chlorpyrifos was found in milk or urine. Approximately 1.7% of the chlorpyrifos fed was found in the feces. Samples were not analyzed for TCP.

Chlorpyrifos has been concluded to be metabolized in animals by oxidation and hydrolysis to phosphoric acid-type compounds and TCP which may be further broken down to CO$_2$. 
However, these studies were performed some time ago, 1973, the metabolism of radiolabeled chlorpyrifos has not been elucidated in a lactating animal or a large animal and other metabolites have been observed in cattle and humans. In cattle fat, a metabolite 0,0,-diethyl-0-(3,6-dichloro-2-pyridyl) phosphorothioate has been detected (J.A.O.A.C. 59, 1081 (1976)) and in human liver, a major metabolite has been identified as similar to chlorpyrifos with a methylthio (-SCH$_3$) group substituted for a chlorine on the pyridinol ring (Ag. Food Chem. 26(1) 118 (1978)). With the identification of these metabolites, further animal metabolism studies are now warranted due to the request to increase the tolerance for residues in goats and sheep. The petitioner should elucidate the metabolism of radiolabeled chlorpyrifos in lactating goats.

Furthermore, if additional metabolites from further plant metabolism studies are judged significant and in need of regulation, animal metabolism studies of these compounds may need to be conducted.

Analytical Methods

Chlorpyrifos

Chlorpyrifos is extracted from soybeans, and soybean forage, straw, meal and hulls (method ACR 73.5.51) by blending with acetone. After filtration and evaporation of the acetone, the residue is partitioned into hexane (soybean oil and soap stock are dissolved directly in hexane), then partitioned into acetonitrile and cleaned up on a silica gel column. The eluate is concentrated. The residue is dissolved in acetone and analyzed by gas chromatography using a flame photometric detector which is highly specific for phosphorus.

Apparent residues on untreated samples ranged from 0.004-0.054 ppm, 0.001-1.93 ppm and 0.001-0.047 ppm for forage, straw and soybeans. Recoveries ranged from 74 to 110% at fortification levels for forage, straw and soybeans of 0.01 to 50 ppm, 0.01 to 5.0 ppm and 0.01 to 0.1 ppm respectively.

3,5,6-Trichloro-2-pyridinol

Residues of TCP are determined by heating soybeans or soybean forage, straw or processed fractions with 10% sodium hydroxide in methanol. Residues of chlorpyrifos and chlorpyrifos intermediate hydrolytic metabolites are hydrolyzed to TCP. Actual TCP residues
are determined by difference. The contribution from chlorpyrifos as determined by an independent method is subtracted.

After blending, the extract is filtered. The filtrate is diluted with water, sodium chloride is added and the solution is washed with diethyl ether-hexane. After acidification, TCP is extracted into diethyl ether-hexane and chromatographed on an acidic alumina column using diethyl ether/pH 6.5 buffer.

From the ether eluate, TCP is partitioned into dilute ammonium hydroxide. After washing with benzene and acidification, TCP is partitioned into benzene. An aliquot of the benzene phase is treated with N,N-bis(trimethyl-silyl) acetamide to form the trimethyl-silyl derivative which is determined by gas chromatography using an electron capture detector.

Apparent residues on untreated samples ranged from 0.012 to 0.110 ppm, 0.004 to 1.19 ppm and 0.003 to 0.093 ppm for soybean forage and straw and soybeans respectively. Recoveries ranged from 72-97% at fortification levels of 0.05-25 ppm TCP and 0.18 and 1.8 ppm chlorpyrifos; 0.05-10 ppm TCP and 0.9 and 1.0 ppm chlorpyrifos; and 0.05 to 1.0 ppm TCP and 0.09 ppm chlorpyrifos for soybean forage and straw and soybeans respectively.

Recovery data is also provided for the processed products: hulls, extracted meal, crude soybean oil, refined soybean oil, refined bleached soybean oil and soap stock. Apparent residues in controls ranged from 0.01 - 0.02 ppm. Recoveries ranged from 80 to 100% at fortification levels of 0.01 to 0.05 ppm chlorpyrifos (chlorpyrifos method) and 0.05 to 0.1 ppm TCP (TCP method) with one sample per residue component per processed product.

Both methods are in PAM II, and EPA has conducted a successful method tryout on a modified method to determine chlorpyrifos residues in or on peaches. Recoveries ranged from 84-94% at fortification levels of 0.025-0.05 ppm. The difference between the method submitted and the method for peaches was the elimination of an extraction step.

EPA performed a successful method tryout using the TCP method on bananas but without the initial alkaline hydrolysis step and partitioning into benzene. Recoveries ranged from 88-94% at fortification levels of 0.05-0.1 ppm.

While recoveries are adequate, apparent residues on untreated controls may be high, approximately 3.00 ppm for soybean straw. The petitioner should either explain why these levels were high, improve the method (the improved method may have to undergo a
method trial) or submit additional data to assure us that some of these reported control residue levels are "outliers."

The method is adequate for obtaining residue data; it cannot be concluded to be adequate for enforcement at this time.

If it is concluded that other metabolites should be regulated, the submission of appropriately validated analytical methods, which may have to undergo a method trial, will be necessary.

Residue Data

Data was obtained from seven field studies in the states of Illinois (2), Mississippi, Michigan, Iowa, Nebraska and North Carolina for soybeans and soybean straw. Green forage residue data was obtained from two studies in Illinois and Mississippi. All applications were apparently by ground rig in combinations of 2, 0.5, 0.5 and 1 lb ai/A; 0.5, 0.5, 1 and 1 lb ai/A; and 2, 0.5, 0.5, 1 and 1 lb ai/A for a total of 3 to 5 lb ai/A in 4 or 5 applications. PHIs ranged from 28 to 51 days for straw and soybeans and from 1 to 22 for green forage. One soybean residue study was performed in Michigan at 4, 1, 1, 2, and 2 lb/A (10 lb/A total).

Residues for soybean forage were 26.4-57.6 ppm at a 1-day PHI, 8.0 to 15.0 ppm at a 7-day PHI, 1.7 to 7.3 ppm at a 14-day PHI and 0.05 to 5.6 ppm at PHI's of 20+ days.

Residues in or on soybeans and straw ranged from non-detectable to 0.82 ppm and 0.5 to 15.4 ppm respectively.

No residue data was submitted for aerial applications. The petitioner should either delete this use from Section B or provide data for forage, straw and soybeans.

Combined residues of chlorpyrifos and TCP in or on soybean forage and straw may exceed the proposed tolerance. Due to the small number of studies reflecting forage and the broad range of residue levels for straw, the petitioner should submit additional residue data reflecting these rac's.

We cannot conclude that the proposed tolerance for soybeans is adequate to cover residues of chlorpyrifos and TCP until questions concerning aerial applications are resolved. The tolerance should reflect all regulated metabolites. The petitioner is advised to collect additional data from the major soybean producing states (Arkansas, Iowa, Minnesota, Missouri and Ohio) reflecting the maximum proposed use, aerial applications and use of the granular
formulation and include analyses for all regulated residues including any significant metabolites found in the additional requested plant metabolism work. If and when the tolerance is established, the tolerance for straw should be expressed in the terms of hay.

A processing study was submitted. Soybeans treated at a total of 10 lb ai/A were processed in a bench scale hexane extraction which is similar to common industrial processes (R. Bischoff, Dow, 2/8/80). The hulls, extracted meal, crude soybean oil, refined soybean oil, refined bleached soybean oil and soap stock were analyzed. Combined residues of chlorpyrifos and TCP were 0.1, 0.13, 0.02, 0.02, <0.05 ppm respectively while residues on the soybeans were 0.14 ppm.

Considering that the sensitivity of the methods (reported as validated at 0.01 ppm and 0.05 ppm chlorpyrifos and TCP respectively), the apparent residue on untreated samples (0.02 ppm) and that data were reported for only one sample, we conclude that residue in meal is at least equal to that of soybeans. We have no assurance that it will not exceed the residue on soybeans and thereby require a food additive tolerance, particularly since in the study submitted the residues on soybeans were far less than the proposed tolerance. The petitioner should submit data for a processing study where soybeans are fortified with chlorpyrifos, TCP and any other regulated metabolites at the proposed tolerance level.

Meat, Milk, Poultry and Eggs

Soybeans and soybean meal, hulls, forage, straw and soap stock are livestock feed items; and soybeans, meal and soap stock are poultry feed items. The petitioner proposes to increase the tolerance for the meat, fat and meat by-products of goats and sheep because of an increase in the dietary burden of chlorpyrifos and TCP from the feeding of alfalfa forage and hay (FF# 0P2281) and soybean forage and straw. We cannot draw a conclusion on the feeding level because of inadequate residue data and questions on the nature of the residue in animals and in both alfalfa and soybeans. Consequently we cannot judge whether existing or proposed tolerances are adequate. A cattle feeding at up to 100 ppm and a hog study at up to 10 ppm appear to be an adequate basis upon which to draw meat and milk conclusions. We will withhold a conclusion on these proposed tolerance increases until these deficiencies for alfalfa and soybean tolerances are resolved.