UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE       April 17, 1979

SUBJECT: CODEX proposal for thiabendazole: tolerances for residues of 0.2 ppm in or on raw grain crops. Caswell #849A.

FROM:     Edwin R. Budd
          Toxicology Branch, HED
          TS-769

TO:       Robert Jaeger
          Toxicology Branch, HED
          TS-769

SUMMARY

In response to your request for a Toxicology Branch opinion on the CODEX proposal for tolerances of 0.2 ppm of thiabendazole (and its 5-hydroxy metabolite) in or on raw grain crops, Toxicology Branch finds that presently available toxicological data on thiabendazole is adequate to support the proposed CODEX tolerances. Toxicology Branch, therefore, would have no objection to the establishment of these proposed tolerances at this time.

BACKGROUND

1. For the purpose of this request, the term "raw grain crops" was considered to include the following crops and food factor (as described in the memo titled "Food Factors", from R. D. Schmitt, Ph.D. to O.E. Paynter, Ph.D., dated October 4, 1977).

<table>
<thead>
<tr>
<th>Grain Crops</th>
<th>lbs/week/household</th>
<th>% Diet (Food factor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corn</td>
<td>2.38</td>
<td>-</td>
</tr>
<tr>
<td>Oats</td>
<td>0.35</td>
<td>-</td>
</tr>
<tr>
<td>Rice</td>
<td>0.54</td>
<td>-</td>
</tr>
<tr>
<td>Rye</td>
<td>0.002</td>
<td>-</td>
</tr>
<tr>
<td>Wheat</td>
<td>10.14</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>13.41</td>
<td>13.70</td>
</tr>
</tbody>
</table>

Total Food Factor for Grain Crops = 13.70%

2. For the purpose of this request, the NOEL used for calculations was 10.00 mg/kg/day which was obtained from a 2-year chronic feeding study in rats (see memo titled "Tolerances for Thiabendazole; Re-assessment of ADI", by R. Engler, Ph.D. to Dr. B. Wilson, dated April 19, 1977).
3. Based on the above, and a safety factor of 100, the following was obtained:

\[
\text{ADI} = 0.100 \text{ mg/kg/day} \\
\text{MPI} = 6.000 \text{ mg/day/60 kg}
\]

Present TMRC* = 1.3338 mg/day/1.5 kg
Present \%ADI* = 22.23%

Incremental increase in TMRC**
   due to CODEX proposal = 0.02556 mg/day/1.5 kg
Incremental increase in \%ADI**
   due to CODEX proposal = 0.43%

* INCLUDES PRESENTLY ESTABLISHED EPA TOLERANCE OF 0.1 ppm IN OR ON WHEAT
** INCLUDES INCREMENTAL INCREASE IN WHEAT (FROM 0.1 ppm TO PROPOSED 0.2 ppm)

See Computer Printout (attached).

4. Relevant toxicological data on thiabendazole is summarized in the attached memo titled "THIABENDAZOLE (TBZ, MEJECT)"

5. Presently available toxicological data is considered adequate to support the proposed CODEX tolerances which would add only 0.02556 mg/day/1.5 kg to the TMRC and only 0.43% to the \%ADI used up (new \%ADI of 22.66%).
<table>
<thead>
<tr>
<th>Crop</th>
<th>Tolerance mg/kg</th>
<th>Food Factor S.F.</th>
<th>ADI mg/kg/day</th>
<th>MPI mg/day/60kg</th>
</tr>
</thead>
</table>
| Apples (2)         | 10.000         | 2.53             | 0.37
| Citrus Fruits (3)  | 10.000         | 3.81             | 0.57
| Peas (116)         | 10.000         | 0.26             | 0.03
| Bananas (7)        | 0.400          | 1.42             | 0.06
| Squash (191)       | 1.000          | 0.11             | 0.01
| Orange, sweet, (154)| 0.250          | 3.64             | 0.03
| Dairy, canned (156)| 0.100          | 20.62            | 0.42
| Beef, red (91)     | 0.100          | 10.11            | 0.16
| Beef, potatoes (157)| 0.025          | 0.40             | 0.01
| Potatoes (127)     | 3.000          | 5.34             | 0.24
| Soybeans (143)     | 0.100          | 0.92             | 0.01
| Wheat (170)        | 0.100          | 10.36            | 0.01

<table>
<thead>
<tr>
<th>MPI mg/day/60kg</th>
<th>1,3338 mg/day/1.5kg</th>
<th>ADI 22.73</th>
</tr>
</thead>
</table>

Current Action - CODEX proposal of 0.3 ppm on all raw grain crops.

Crop | Tolerance mg/kg | Food Factor S.F. | mg/kg/1.5kg
--- | --------------- | ----------------- | ------------
Grain | 0.300 * 13.70   | 0.04110          |
Wheat | 0.1554          | 0.02556          |

Total increase in TMRC = 0.02556

includes wheat at 0.2 ppm

<table>
<thead>
<tr>
<th>MPI mg/kg/1.5kg</th>
<th>TMRC 22.66</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3338</td>
<td>22.66</td>
</tr>
</tbody>
</table>
Conclusions and Suggestions

A survey of Toxicology Branch files, Chemistry Branch petition files and readily accessible informational resources revealed the following about Thiabendazole.

1. Thiabendazole has long been recognized as an anthelmintic against parasitic worms in humans and domestic animals. The maximal daily dose for humans according to The United States Dispensatory (27th edition, 1973), in which it is listed, is 3 grams per day.

2. Thiabendazole (and/or its metabolite, 5-hydroxythiabendazole) has tolerances ranging from 0.1 ppm on meats, meat byproducts, fat and milk to 10 ppm on apples, pears citrus fruits and sugar beet tops. See 40 CFR 180.262.

3. Relevant toxicological data on Thiabendazole include:

Feeding Studies
   (a) 30-Day Subacute Feeding, Rats
       NOEL < 100 mg/kg/day
   (b) 6-Month Subacute Feeding, Rats
       NOEL = 50-100 mg/kg/day
   (c) 2-Year Chronic Feeding, Rats
       NOEL = 10 mg/kg/day (TB Memo by R. Engler, Ph.D., 4/19/77)
       Negative for oncogenic effects
   (d) 2-Year Chronic Feeding, Rats
       Negative for oncogenic effects
   (e) 2-Year Chronic Feeding, Dogs (Merck
       NOEL = 20-100 mg/kg/day
   (f) 2-Year Chronic Feeding, Dogs (Wyboad
       NOEL = 50 mg/kg/day
   (g) 14-Week Subacute Feeding
       NOEL < 156 mg/kg/day lambs
       NOEL = 15-46 mg/kg/day swine
       NOEL = 89-267 mg/kg/day calves
   (h) 16-Week Subacute Feeding, Sheep
       NOEL = 10-50 mg/kg/day
   (i) 50-Week Subacute Feeding, Sheep
       NOEL = 30-50 mg/kg/day

Oncogenic Studies
   (a) See 2-Year Chronic Feeding, Rats (2 studies, above)
   (b) 18-24 Month Oncogenic Study, Mice (In Progress)
       Currently being performed by Merck, Sharpe & Dohme

Teratogenic Studies
   (a) Teratology Study, Rats
       0 and 80 mg/kg/day on days 8-15 of gestation
       Negative for terata
(b) Teratology Study, Rabbits
0, 100, 200, 400 and 800 mg/kg/day on days 8-16 of gestation
Negative for terata.

Reproduction Studies
(a) Rats, 3-Generations, 2 Litters/Generation
0, 20, 40 and 80 mg/kg/day
NOEL = 40 mg/kg/day (?)
(b) Mice, 5-Generations
NOEL = 150 mg/kg/day
(Also negative for terata)

Inhalation Study
(a) 31-Day Subacute Inhalation Study, Mice
Fine dust, 6 hours/day, 5 days/week
Single dosage level of 70 mg/m^3 (or 0.07 mg/L) produced
no effects.

Metabolism Studies
(a) Man
14 or 28 mg/kg orally. 87-100% of dose recovered in urine
(90-101%) and feces (4-9%) within 48 hours. Nearly all of
urinary products were metabolites. Major metabolite was
5-hydroxythiabendazole (with conjugation to glucuronide
and sulfate).
(b) Rats, Dogs, Cattle, Sheep, Goats, Swine.
Findings were very similar to those obtained in man. Tissues
taken several days after treatment were virtually free of
thiabendazole and/or metabolites.

(4) Data gaps for Thiabendazole include:
Mutagenicity studies

Data Examined
(2) 40 CFR 180.242
(3) Toxicology Branch Caswell, subject and petition files
(4) Toxicity Profile (Contractor--dated 10/4/78)
(5) Registry of Toxic Effects of Chemical Substances 1977 (NIOSH)
(6) Suspected Carcinogens 1976 (NIOSH)
(7) Accession 7095267, 008323, and 095266
Attachments

(2) 40 CFR 180.252 (1977)
(3) Toxicity Profile (Contractor--dated 10/4/78)
(4) Toxicology Branch Memo by R. Engler, Ph.D. (dated 4/7/77 and 4/19/77) and by Orville Paynter, Ph.D. (dated 4/19/77)
Thiabendazole is a compound of theophylline and methylamine which contains about 75 percent of theophylline (approximately the same as in amophyl- line); it is used for the same purposes as amophylline.

Dipyridamol, also called dipyridyl, is 2-(2,3-dihydroxypropyl)theophylline, and contains about 70 percent of anhydrous theophylline. It is a white, amorphous powder, freely soluble in water and sparingly soluble in alcohol; its aqueous solution is essentially neutral. When administered orally it produces less nausea than amophylline and other alkaline theophylline compounds; therefore it can be given in larger doses than amophylline. Dipyridamol has the peripheral vasodilator, bronchodilator, diuretic, and myocardial stimulant actions of amophylline and other theophylline derivatives. It may be administered orally or intravenously. The usual oral dose for adults is 200 mg. 3 or 4 times daily, which may be increased to 400 mg. 3 times daily when necessary. For treatment of an acute asthma attack or cardiac dyspnea, 500 mg. may be administered intravenously, very slowly, and repeated if necessary. The usual oral dose for children is 14 mg. per kg. of body weight daily, given in 3 or 4 divided doses. Dipyridamol is available in elixir, injection, and tablet dosage forms under the trademarked names Dilor (Savage), Lusylin (Malinckrodt), and Norephyl (Lemmon).

Oxtripryline is choline theophyllinate, also called theophylline choline. It is a combination of molecular equivalents of theophylline and choline, and contains about 64 percent of theophylline. It is a white, crystalline powder, very soluble in water and freely soluble in alcohol; its aqueous solution is alkaline. Reports of improved gastrointestinal absorption and tolerance, compared to amophylline, have been published, but a comparison with other theophylline compounds has not come to our attention. Oxtripryline is administered orally in conditions for which amophylline and other theophylline derivatives may be used. The usual range of dose for adults is 100 to 400 mg. 4 times daily, after meals and at bedtime. The dose for children 2 to 12 years of age is 3.6 mg. per kg. of body weight 4 times daily. Oxtripryline is available in tablets containing 100 and 200 mg, under the brand name Choleryl (Warner-Chilcott).

Thiabendazole is 2-(4-thiazolyl)benzimidazole and contains, on the hydrochloric acid basis, not less than 99.0 percent of C₁₈H₁₄N₂S (201.25).

Thiabendazole may be prepared by interactions involving o-nitroaniline and 4-thiazolecarbonyl chloride as
Thiamine Hydrochloride—Thiamine Mononitrate


Description.—White to practically white powder; odorless or practically odorless. Practically insoluble in water; 1 Gm. dissolves in about 150 ml. of alcohol and 300 ml. of chloroform; very slightly soluble in ether. Melt between 296° and 301°.

Actions and Uses.—Thiabendazole is an anthelmintic active against a variety of helminths. It is useful in the treatment of ascariasis (large roundworm infection), creeping eruption or cutaneous larvae migrans (infection of the skin of man caused by the larvae of the dog and cat hookworm, Ankylostoma braziliense, and A. caninum), enterobiasis or oxyuriasis (Enterobius vermicularis or pinworm infection), strongyloidiasis (Strongyloides stercoralis or threadworm infection), trichinosis (Trichinella spiralis infection), trichuriasis (Trichuris trichiura or whipworm infection), and uncinariasis or ancylostomiasis (hookworm disease due to Necator americanus or Ancylostoma duodenale). Thiabendazole is the drug of choice in the treatment of creeping eruption and strongyloidiasis. It is considered highly effective against Enterobius vermicularis infection. It reduces symptoms of trichinosis but it does not appear that it will eliminate the adult Trichinella spiralis. In the treatment of hookworm disease due to *Necator americanus*, thiabendazole appears to be as effective as tetrachloroethylene; against *Ancylostoma duodenale*, thiabendazole may be more effective and less toxic than tetrachloroethylene. In the treatment of *Trichuris trichiura* infection a variable effectiveness is reported but it is considered a preferred drug. Results in the treatment of ascariasis (Ascaris lumbricoides infection) have been variable unless high dosage is used; piperazine crotate may be the drug of choice in this infection (Milette et al., in Harrison’s Principles of Internal Medicine, 6th ed., 1970).

Thiabendazole is rapidly absorbed from the gastrointestinal tract; maximum plasma levels are attained 1 to 3 hours after oral administration, and within 48 hours about 90% of the metabolites of the drug have been excreted in the urine. Food in the digestive tract is claimed not to have any effect on the action of the drug, and purgation prior to treatment is not necessary.

Undesirable Effects.—Dizziness, anorexia, nausea, vomiting occasionally; diarrhea, fever, abdominal distress, flushing, chills, angioedema edema, pruritus, lethargy, perianal rash, skin rash, and headache occur less frequently. Tinnitus, hypotension, and collapse, and also numbness, hyperpyrexia, and anoxia have been reported. It is possible that some undesirable effects occur as a result of sudden destruction of large numbers of parasite and absorption or released toxic organic material. Also, some of the effects may be caused by penetration of the gut by the parasite and migration into the lungs as a result of stimulation by thiabendazole; this may occur with ascariasis, necessitating close supervision of patients with ascariasis.

Warnings and Precautions.—The lachrymatory potential of thiabendazole requires that it be used with caution in patients with liver disease or impaired liver function.

Although studies on animals have failed to reveal evidence of teratogenicity, use of thiabendazole in pregnant women should be undertaken only if the possible beneficial effect outweighs the possibility of damage to the fetus.

Dose.—The usual dose, given orally, is 25 mg. per Kg. of body weight twice daily. This dosage is given for 1 or 2 days in the treatment of strongyloidiasis, uncinariasis, and ascariasis. In trichuriasis the same dosage is given for 2 to 4 days, in cutaneous larva migrans for 2 days, in enterobiasis for 1 day and repeated in 7 days, and in trichinosis for 2 to 4 days. The maximal daily dose is 3 Gm.

Dosage Form.—Suspension containing 500 mg. in 5 ml.

Thiamine Hydrochloride

Thiamine mononitrate

Thiamine hydrochloride contains, on the dry basis, not less than 98.0 percent of C_{6}H_{5}N_{2}O_{6}HCl (337.27). Thiamine mononitrate contains, on the dry basis, not less than 98.0 percent of C_{6}H_{5}N_{2}O_{6}S (327.36). The structural formula of the hydrochloride is

![Structural formula](image)

Thiamine Hydrochloride: Anserine hydrochloride; thiamine chloride; vitamin B_{1}, hydrochloride. Thiamine, Mononitrate: Anserine nitrate; thiamine nitrate; vitamin B_{1}, mononitrate.

Vitamin B_{1} was first isolated in crystalline form from rice bran by Jansen and Donath, in 1926, who named it 'anerin'. Its empirical formula was determined by Windaus and his collaborators in 1932 and Williams and Cline in 1936 announced its synthesis (J.A.C.S., 58, 1504, 1936). For a method of synthesizing the pyrimidine and thiazole moieties of thiamine, and of combining them, see Cline et al. (J.A.C.S., 59, 1052, 1937).

Thiamine hydrochloride and thiamine mononitrate represent two different types of salts of thiamine. In the hydrochloride, 1 molecule of thiamine is combined with 2 chloride ions; in the mononitrate, 1 molecule of thiamine is combined with 1 nitrate ion. The reason is that in the hydrochloride the NH_{2} of the pyrimidine moiety is positively charged by acceptance of a proton, and since the thiazole nitrogen is quaternary, 2 chloride ions are required for the doubly-charged cation. In the mononitrate, the only charge is on the thiazole nitrogen, and a single nitrate ion suffices for electrostatic neutralization. An important difference in the properties of the salts is that the hydrochloride is acid in solution, the pH being about 3, while the mononitrate is practically neutral, the pH being close to 7.

Description.—Thiamine Hydrochloride: Small, white crystals or crystalline powder, usually having a slight characteristic odor. When exposed to air, the anhydrous
Chapter I

Environmental Protection Agency

§ 180.227  Methylsulfonil - 2, 6-dinitro-N,N-dipropylaminine; tolerances for residues.

Tolerances are established for negligible residues of the herbicide 2, 6-dinitro-N,N-dipropylaminine in or on the raw agricultural commodities: almonds, almond hulls, broccoli, Brussels sprouts, cabbage, cauliflower, cottonseed, cucumbers, melons, soybeans (dry form), and stone fruits at 0.1 part per million.

(37 FR 1929, July 12, 1972)

§ 180.228  Propiconazole and its metabolites; tolerances for residues.

Tolerances are established for negligible residues of the herbicide propiconazole in or on the raw agricultural commodities: sugar beets (roots and tops) and tomatoes at 0.1 part per million.

§ 180.229  Phosphamidon; tolerances for residues.

Tolerances (expressed as phosphamidon) for residues of the insecticide phosphamidon (2-chloro-2-diethylcarbamoyl-1-methylvinyl dimethyl phosphate) including all of its related chemical inhibitors and in agriculture commodities are established as follows:

1 part per million in or on apples, 0.75 part per million in or on grapefruit, lemons, oranges, tangerines, 0.5 part per million in or on broccoli, cauliflower, cucumbers, peppers, 0.25 part per million in or on cantaloupes, watermelons, 0.1 part per million in or on cottonseed, tomatoes, sugarcane, tomatoes and peanuts.

§ 180.230  S-Propyl dipropylthiocarbamate; tolerances for residues.

Tolerances are established for negligible residues of the herbicide S-propyl dipropylthiocarbamate in or on the raw agricultural commodities: corn, corn fodder and forage, fresh corn including sweet corn (kernels plus cob with husk removed), peanuts, peanut forage, peanut hay, potatoes, soybean forage, soybean hay, soybeans, and sweet potatoes at 0.1 part per million.

(37 FR 2829, June 6, 1971)

§ 180.231  S-(4-O-Diisopropyl phosphorodichloride) of N-(2-mercaptoethyl) benzenesulfonamide; tolerances for residues.

Tolerances are established for negligible residues of the herbicide S-(4-O-diisopropyl phosphorodichloride) of N-(2-mercaptoethyl) benzenesulfonamide in or on the raw agricultural commodities: carrots, cottonseed, cucumbers, fruiting vegetables, leafy vegetables, and onions (dry bulb) at 0.1 part per million.

§ 180.232  Thiabendazole; tolerances for residues.

(a) Tolerances are established for residues of the fungicide thiabendazole (2,4-thiazolyl benzimidazoles) in or on the following raw agricultural commodities:

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Parts per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apples (post-h)</td>
<td>10</td>
</tr>
<tr>
<td>Bananas (post-h)</td>
<td>2</td>
</tr>
<tr>
<td>Bananas, pulp (post-h)</td>
<td>0.4</td>
</tr>
<tr>
<td>Beets, sugar (post-h)</td>
<td>2</td>
</tr>
<tr>
<td>Citrus fruits (post-h)</td>
<td>2</td>
</tr>
<tr>
<td>Garbers (post-h)</td>
<td>2</td>
</tr>
<tr>
<td>Potatoes (pre and post-h)</td>
<td>3</td>
</tr>
<tr>
<td>Soybeans</td>
<td>1</td>
</tr>
<tr>
<td>Squash, Hubbard</td>
<td>1</td>
</tr>
<tr>
<td>Wheat, straw</td>
<td>2</td>
</tr>
</tbody>
</table>

(b) Tolerances are established for combined residues of thiabendazole and its metabolite 3-hydroxythiabendazole in the following raw agricultural commodities:

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Parts per million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle, ft.</td>
<td>0.1</td>
</tr>
<tr>
<td>Cattle, mbp</td>
<td>0.1</td>
</tr>
<tr>
<td>Cattle, md</td>
<td>0.1</td>
</tr>
<tr>
<td>Goats, nt</td>
<td>0.1</td>
</tr>
<tr>
<td>Goats, mbp</td>
<td>0.1</td>
</tr>
<tr>
<td>Goats, md</td>
<td>0.1</td>
</tr>
<tr>
<td>Hogs, ft</td>
<td>0.1</td>
</tr>
<tr>
<td>Hogs, md</td>
<td>0.1</td>
</tr>
<tr>
<td>Hogs, mbp</td>
<td>0.1</td>
</tr>
<tr>
<td>Horses, ft</td>
<td>0.1</td>
</tr>
<tr>
<td>Horses, mbp</td>
<td>0.1</td>
</tr>
<tr>
<td>Horses, md</td>
<td>0.1</td>
</tr>
</tbody>
</table>
§ 180.243
Commodity Parts per million
Horses, meat........ 0.1
Milk................ 0.1
Sheep, fat........... 0.1
Sheep, mbp........... 0.1
Sheep, meat........ 0.1

§ 180.213 2-Chloro-4,6-bis(isopropylamino)-s-triazine; tolerances for residues.
A tolerance of 0.25 part per million is established for negligible residues of the herbicide 2-chloro-4,6-bis(isopropylamino)-s-triazine in or on the raw agricultural commodities sorghum grain, forage, and fodder.

§ 180.211 Basic zinc sulfate; tolerances for residues.
A tolerance of 30 parts per million is established for negligible residues of the fungicide basic zinc sulfate, calculated as elemental zinc, in or on the raw agricultural commodity peaches.

§ 180.215 Streptomycin; tolerances for residues.
Tolerances of 0.25 part per million are established for negligible residues of the fungicide streptomycin in or on the raw agricultural commodities celery, peppers, and tomatoes from treatment of the seedling plants before transplanting; potatoes from treatment of seed pieces; and pome fruits.
(38 FR 31559, Nov. 15, 1973)

§ 180.216 Daminazone; tolerances for residues.
Tolerances are established for residues of the plant regulator daminazone (butanedioic acid mono (2,2-dimethylhydrazide)) in or on raw agricultural commodities as follows:
50 parts per million in or on sour cherries.
50 parts per million in or on plums (fresh prunes).
40 parts per million in or on tomatoes.
30 parts per million in or on apples, peaches, peaches, peanuts, and sweet cherries.
20 parts per million in or on Brussels sprouts, peanut hay, and peas.

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10 parts per million in or on grapes and peanut hulls.
3 parts per million in or on melons.
2 parts per million in poultry kidney.
1 part per million in or on hoppers.
0.2 parts per million in the meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry (except poultry kidney), and sheep.
0.2 part per million in eggs.
0.02 part per million in raw agricultural commodities sorghum grain, forage, and fodder.

§ 180.247 2-Chloroallyldiethyldithiocarbamate; tolerances for residues.
Tolerances are established for negligible residues of the herbicide 2-chloroallyldiethyldithiocarbamate in or on the raw agricultural commodities bean vines, brocoli, brussels sprouts, cabbage, cantaloups, cauliflower, celery, chives, chilis, collards, corn (kernels plus cob with husk removed), corn fodder and forage, corn grain, cucumbers, endive (escarole) kale, lettuces, lima beans, mustard greens, okra, potatoes, snap beans, soybeans, soybean forage and hay, spinach, tomatoes, turnip greens, turnips, and watermelons at 0.2 part per million.

§ 180.250 3-P-methyluracil
A tolerance is established for the herbicide 3-P-methyluracil in or on the raw agricultural commodities.

§ 180.251 Daidzein-2-toluenesulfonyl chloride; tolerances for residues.
Tolerances are established for the herbicide daidzein-2-toluenesulfonyl chloride in or on the raw agricultural commodities.
0.1 part per million in or on raw agricultural commodities sorghum grain, forage, and fodder.
0.1 part per million in or on raw agricultural commodities.
0.1 part per million in or on raw agricultural commodities sorghum grain, forage, and fodder.

§ 180.248 Neodecanic acid; tolerances for residues.
A tolerance of 1 part per million is established for negligible residues of the desiccant and defoliant neodecanic acid (a mixture of 10-carbon trialkyl acetic acids (calculated as CH₃COOH)) in or on the raw agricultural commodity cottonseed.

§ 180.249 Alachlor; tolerances for residues.
Tolerances are established for combined residues of the herbicide alachlor (2-chloro-2',6'-diethyl-N-ethylcarboximidamide) and its metabolites (calculated as neopentyl) in or on the raw agricultural commodities as follows:
3 parts per million in or on peanut forage and hay.
Two year feeding study—rats: Charles River weanling albino rats were fed thienobendazole (purify unspecified—Lot no. L-5752/6-0-05) at 20, 40, and 80 mg/kg/day starting one week after weaning, for 102-107 weeks. This is a study similar to the one above. No effects were noted which were attributable to the thienobendazole for survival, time of death in non-survivors, neoplasms incidence or location and tissue histopathology. At either the 10 and 20 mg levels, there were no effects on weight gain, food consumption, or hemoglobin and hematocrit values; these were only effects attributable to thienobendazole administration.

Two year feeding study—dogs: Purchased beagle dogs were fed by gelatin capsules, 0, 20, 40, and 80 mg/kg daily for 102 weeks to 2 males and 3 females in each dose level. Purify of thienobendazole was unspecified (Lot L-5852/6-0-05). At the 20 and 40 mg/kg/day levels, no effects attributable to thienobendazole were noted on survival, weight gain, general condition, organ weights, hematological or clinical chemistry values, and histopathological observations. In ten dogs at the 80 mg level, a small amount of impurities material was found adhering to the gall bladder wall.

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**Dead/Alive**

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25/10</td>
</tr>
<tr>
<td>120 mg/kg/day</td>
<td>30/5</td>
</tr>
<tr>
<td>80 mg/kg/day</td>
<td>27/8</td>
</tr>
</tbody>
</table>

*About 26% of deaths and animals sacrificed in nonhumid condition occurred after 70 weeks of the study and was attributed to the age of the rats.
At the 125 mg/kg level, two of six dogs died and there was slight weight loss, slight to moderate reduction in hemoglobin and hematocrit value, increased frequency of urinary albumin, moderate chronic inflammatory liver changes, slight liver glycogen depletion, and impeded material adhering to the gall bladder mucosa with no evidence of extraneous material in the bile ducts.

One nonsurviving dog exhibited cirrhosis of the liver of a type not due to biliary obstruction. Prior to death this animal had ele- 
terated blood urea nitrogen, serum alkaline phosphatase, and serum glutamic pyruvic transaminase values. The relationship between thiosalendazole doses and these signs is uncertain.

Toxicology

50 (Charles River) albino female rats, weighing 260g at initiation of experiment, were administered oral doses of 0.19 (10 rats) and 5.4 (8 rats) mg/kg byavage as a 1:5 suspension at volumes of 5ml/kg live weight from 4th to 15th day of gestation. Purity of thiosalendazole unspecified.


2. Reproduction and viability: Reproductive capacity of both groups were normal. Mean implantation was slightly higher in control (14.2) than in treated groups (13.3) and live litter size was slightly higher in control (23.3) than in treated group (12.7). Fetal rates were the same for both groups.

3. Fetal observations: Average fetal weights the same. Sex distribution not noted but no external or internal anomalies observed. Treated group had 6.6% external and 14.6% internal anomalies, the latter being essentially "skeletal variation". Total absence of embryotoxic effects.

An oral dose of 60.5 mg/kg for 7 days during gestation on Charles River albino rats was not teratogenic.

Pregnant New Zealand albino female rabbits were administered thiosalendazole orally from the 5th through the 16th day of gestation at dose levels of 0, 100, 200, 400, and 800 mg/kg/day in four different studies. The first study used 100 rabbits with 4 control and 16, 27, 46 and 47 rabbits at the 100 to 800 mg/kg/day levels. Daily administration of thiosalendazole in a 1% suspension in 1% ethanol followed by a 10% ethanol rinse. The greater incidence of stillbirth and death during these studies are attributed to this stressful administration (stomach tube) rather than to thiosalendazole.

Body weight: There was an increasing loss of weight in the pregnant rabbits from day 1 to day 17 of gestation at 200 (+/−), 400 (+/−), and 800 (+/−) mg/kg/day dose levels and a 30% weight gain for both the control and 100 mg/kg/day dose level. In both studies, the post partum weight changes (day 17 to 24 and 30), especially at the 400 mg/kg level, were markedly higher than the controls. The net result of weight changes from day 1 to 24 and 30 of gestation were not appreciably different between control and treated groups.
b. Reproduction and viability: Although not stated to be significant, the percent animals surviving in those bred varied from 99% in controls to 69% at 750 ppm and the percent dose delivered to those bred varied from 93% in controls to 50-60% in the treatment groups (29). The mean body weight at necropsy in the control was 5.5 and average for treatments 17.5 which was found not to be statistically significant. Average number of implants / animal was the same in control and average weight of viable fetuses slightly lower in treatment groups.

c. Fetal observations: Average weight of viable fetuses was slightly lower in treatment groups but insignificant. Primary anomalies noted were skeletal variations, but these abnormalities were similar in controls and common to rabbit colony. Abnormalities not related to treatment and there was a lack of dose response.

Thiabendazole does not appear to have teratogenic properties at dosages used.

d. Generation Reproduction

F1 (29) and female (26) mature albino rats (F0) were assigned to 3 control and 3 treatment groups containing 10 males and 16 females each, at 30 days of age. They were fed by intramuscular dose 1, 20, 30 and 50 ppm daily weight of thiabendazole (proprietary unspecified) in 0.5% CMC solution to give a solution/kg body weight. Doseage given to each side through stomach station and weighing of the first litter and to males through ration and the females through weighing of the second litter. The pups were not used until 25 days of age (except through day’s milk up to 21 days). Generation females delivered two litters (Litter 1 and Litter 2) and their pups to weighing (21 days). F1 generation was added incorporation of thiabendazole into the basal diet (proprietary unspecified) at levels above. Same procedure for F2, Litter 1 pups, at 100 days of age, dietary age was discontinued and dosage was by gastric intubation.

a. Body weight: For durations of 10 weeks, both body weight gain and food intake were lower in proliferative treatments than in controls of males in both F1 and F2 generations only in females in the F2. However, efficiency of food utilization were similar in all groups of same body weights of F3 rats at 25 days of age were similar in all groups.

b. Hematology: Hematological data all normal for F1 and F2 rats compared to pre-treatment F1 rats at 106 days of age and F3 at 22 days of age at similar treatment level.

c. Urinalysis: No significant differences between the generations for any dose levels for specific gravity or pH.

d. Reproduction and viability: No abnormalities of pups observed in any of the dose levels for Litter 1 and 2 of F1, F2, F3, and F4 generations nor were there any apparent differences in other reproduction and lactation responses attributable to thiabendazole.

e. Pathology: Prostate gland weight increase of 23 and 25% as percent of body weight and 21 and 25% on dose weight basis between controls and 50 and 75 ppm, respectively.
reverse was true in the F2 generation where smaller prostate gland weights were statistically different from the control on a weight basis but not on percent of body weight basis. In F2, testis weights in all three treatments were significantly larger in a percent of body weight basis. This data may reflect the statistically significant smaller body weights of the F2 males at the 30 and 80 mg/kg dose levels.

c. Histopathology: The differences cited under pathology did not indicate biological difference since no significant structural changes were revealed. No treatment related pathological manifestations were found in rats given thiamazole.

Doses of 70, 40 or 80 mg/kg body weight over F0 to F3 generation indicated thiamazole is not a teratogen.

* Food and Drug Research Labs, Haspeth, N.Y.

Data Gap:

Mutagenicity

Reference:

EPA files Sec. Reg. 650171, 641622, 0022912, 004735, 229287, 161773, 116571, 272759, 227729, 107852, 109572, 004735, 123797, 004735, 541730


October 4, 1973

Robert A. Zinggeman, Ph.D.

Richard L. Johnson, Ph.D.

Reginald A. Norkin, M.D.
SUBJECT: Tolerance for Thiabendazole 430 ppm on Sugarbeets
       (from post harvest application)

FROM: Toxicology Branch

TO: E. Wilson
    Product Manager
    Chemistry Branch

Pesticide Petition: GF1860 and 5F1646

Petitioner: Merck Co.

Conclusion: The requested tolerance on sugar beets and the previously requested tolerance of 0.1 ppm on soybeans can be established, provided that an assurance is obtained from the petitioner that a second genotoxicity study (second species) will be submitted within a reasonable time span, and interim reports of this study will be submitted as they become available. (The usual time required for such an genotoxicity study is 2.5 to 3 years). Furthermore, mutagenicity testing must be carried out, or initiated at the time when requirements become finalized. This conclusion is reached because:

The studies submitted previously show that thiabendazole is not oncogenic for the rat, is not a teratogen, and does not affect reproduction, and

The requested tolerances on sugar beets and soybeans will not add an appreciable amount, if any, to the dietary burden of an; see also determination of MRL and maximal theoretical exposures (MTE) calculation in review.

Note: The previous recommendation, not to establish the soybean tolerance (memo of October 29, 1976) was based solely on the concept of a data gap with respect to proposed data requirements.

Review

New toxicity data were submitted. We refer to our reviews of September 2, 1975; and October 28, 1976 (PPP 5F1646). For convenience, the toxicity tests are listed below; thiabendazole also has a history of anthelminthic drug.

LD50 (rat) 3.33 g/kg
LD50 (mouse) 3.81 g/kg
Subacute feeding (rat) MRL 100 mg/kg; dose: finding study 301, and 180 days,
30% deaths at 1400 mg/kg
Teratology (rats) Negative at 80 mg/kg/day;
             0-15th day of pregnancy

[Signature]
2-year rat feeding
2-year dog feeding
5-generation reproduction
(mouse)

ADI, HPI, and MTE

Based on the rat 2-year feeding study the ADI for man (100X safety factor) is 0.4 mg/kg.b.w./day which results in a HPI for a 60 kg man of 24 mg/day.

Tolerances for thiabendazole are established for the following rac (180.242):

10 ppm apples, citrus, pears, sugarbeet tops
3 ppm bananas (0.4 ppm in pulp)
1 ppm hubbard squash
0.25 ppm sugarbeets
0.1 ppm milk; meat, fat and meat byproducts, cattle, goats, hogs, horses and sheep.
0.02 ppm sweet potatoes.

Using the appropriate food factors the MTE (maximum theoretical exposure) of man is calculated to be 0.982 mg/day or about 1% of the HPI, the ADI is therefore not exceeded.

[Signature]

Engler, Ph.D.
Toxicology Branch
Registration Division

4/19/77
The previous calculation of the ADI and thus the maximum permissible intake for man was based on a SEL of 0.5 mg/lb/day in a rat study. Discussions between the petitioner and officials of FDA however established that this level was in fact not a true SEL since severe growth depression occurred at this level. The SEL was thus set at the next lower feeding level, namely 0.1 mg/lb/day. This will reduce the ADI from 0.5 mg/lb/day to 0.1 mg/lb/day and the SDI from 25 mg/day to 5 mg/day. This change, however, does not affect our previous conclusion about the safety of the proposed tolerances since this lowered ADI and SDI respectively is not exceeded by the existing and the proposed tolerances which result in a maximum theoretical exposure of roughly 1.0 mg/day.

[Signature]

[Name]

Toxicology Branch
Registration Division
II. 11, 1977

To: R. N. Caswell

From: Y. Pope

Subject: Briefing Memo for Thiabendazole - tolerance

Of: 4.1 ppm in/on Soybeans (57756)

Office of Registration

Thiabendazole Branch (R-41)

C. J. Wilson (R-42)

Registration Division (R-557)

ADD: Associate Director for Scientific Review

Registration Division (R-557)

This memo addresses two points in your briefing memo concerning the 4.1 ppm tolerance in soybeans for thiabendazole: 1) demonstration of "safety" of proposed tolerance and 2) the need for delayed neurotoxicity tests.

1) Sufficient toxicological data has been submitted by the petitioner to satisfy all requirements for tolerances prior to the need for mutagenic and an additional (second) oncogenic studies. Thiabendazole is used in veterinary medicine at high levels of intake. No evidence, of which the TOX Branch is aware, has implicated the compound as producing any unreasonable adverse effect in humans or at the current tolerance levels. On the basis of long-term feeding studies we have established a NOEL of 3 mg/kg/day and an ADI of 0.006 mg/kg/day. This gives an RDI of 0.1 mg/kg/day. A tolerance of 4.1 ppm in soybeans is calculated to produce a TMD to the average daily diet of 0.973 mg/kg/day (0.1 x 1.92 x 0.973). The TMD of this tolerance and existing tolerances is approximately 1 mg/kg/day. This is below the RDI and the ADI. It is the opinion of the TOX Branch that the added 0.973 mg/kg/day or the requested soybean tolerance will not add a significant risk to man, even without the second oncogenicity study. The second oncos study is not being validated and is required. The potential significance of the second oncos study is not serious enough to disqualify this soybean tolerance.

2) Thiabendazole contains no organic phosphate or carbonate toxicity and therefore a delayed neurotoxicity test is not required by Sec. 3 regulations. In addition, we know of no theoretical grounds or data to suspect that thiabendazole would cause delayed neurotoxicity. The study in the opinion of the TOX Branch is unnecessary.

Best Available Copy

ENR E. Payne, Ph.D.

R. N. Caswell

3/11/77