The E. I. duPont de Nemours and Company Inc. proposes the establishment of temporary tolerances for residues of herbicide 2-chloro-N[4-methoxy-6-methyl-1,3,5-triazine-2-y1]-aminocarbonyl] benzenesulfonamide (DPX-4189) in or on wheat grain, barley grain, oats grain and rye grain at 0.05 ppm.

This petition constitutes the first request for tolerances for residues of this chemical. The temporary tolerances are intended to be used in conjunction with Experimental Use Permit No. 352-EUP-105. The proposed EUP will entail the application of up to 8000 lbs of DPX-4189 to 82000 acres of wheat, barley and reduced tillage fallow between March 1, 1981 and July 1, 1983.

Conclusions

1. The molecular weight of the inert ingredient must be given in order to permit a determination as to whether this inert is cleared under is cleared under

2. The fate of DPX-4189 is adequately delineated for the purposes of this experimental use.

3. Adequate analytical methods are available to enforce the proposed tolerances.

4a. No detectable residues of DPX-4189 are expected in wheat or barley grain. The proposed temporary tolerances of 0.05 ppm for wheat and barley grain are adequate.
4b. Since the proposed use involves applications to wheat and barley only, Section F should be amended to delete the proposed temporary tolerances for oats and rye grain.

4c. Since residues are non-detectable in wheat and barley grain, residues in milled fractions are not expected to exceed that on the r.a.c.'s. Therefore, food additive tolerances are not necessary.

5. There will be no problems with secondary residues in meat, milk, poultry and eggs from this limited experimental use.

**Recommendation**

For reasons listed in Conclusions 2 and 4b, we recommend against the proposed temporary tolerances. We could recommend favorably for the proposed temporary tolerances on wheat and barley grain provided that the inert and provided Section F is amended to delete the proposed temporary tolerances for oats and rye grain.

For a future permanent tolerance the following will also be required:

1. Analysis of technical DPX-4189 for nitrosamines.

2. Additional metabolism studies. In particular, the nature of the residue in the straw of wheat and barley should be elucidated.

3. If the above metabolism studies indicate the presence of metabolites of DPX-4189 in wheat and barley plants which are of toxicological concern, analytical methods for these metabolites will be necessary.

4. If wheat or barley straw is found to contain metabolites of DPX-4189 which are of toxicological concern, large animal (ruminant) metabolism/feeding studies will be needed.

**Detailed Considerations**

**Manufacture and Formulation**

DPX-4189 is manufactured by:

Technical DPX-4189 is at least 91% pure. Impurities and their concentrations are as follows:
We would not expect a residue problem from any of these impurities.

DPX-4189 is formulated as DuPont DPX-4189 DF Weed Killer, a dry flowable powder containing 82.5% active ingredient. One of the inert ingredients may not be cleared for this use. The molecular weight of this inert must be given since

For a permanent tolerance technical DPX-4189 should be analyzed for the presence of nitrosamines.

Proposed Use

DPX-4189 DF Weed Killer will be mixed with water and applied as a spray.

The rates of application will be as follows:

Barley (Spring and Winter)
Post-emergence only before "boot" stage. A single application of 0.125-1 oz product (0.1-0.83 oz act) per acre.

Wheat (Spring and Winter)

Pre-emergence - A single application of 0.25-0.75 oz product (0.21-0.62 oz act) per acre.

Shallow Postplant Incorporated - A single application of 0.125-1 oz product (0.1-0.83 oz act) per acre. Apply before "boot" stage but not within 1 month of pre-emergence or post-plant incorporated treatment.

Reduced Tillage Fallow-Wheat or Barley

Make a single application of 0.5-2 oz product (0.41-1.65 oz act) per acre to the stubble either in the fall after harvest or in early spring.

There is a restriction against grazing treated areas and feeding treated forage to livestock.
Nature of the Residue

In Plants

In a greenhouse study, wheat was treated postemergence with phenyl labeled 14C-DPX-4189 at 1.8 oz act/A (2x the max. proposed rate) and 0.45 oz act./A (1/2 the max proposed rate). When the wheat reached maturity the stalks and foliage were air dried and samples of grain, hulls and straw were analyzed for total 14C-residue. Less than 0.01 ppm of 14C-residue (calculated as DPX-4189) was detected in wheat grain and hulls and only 0.10-0.13 ppm was found in dry straw. In order to determine the nature of the radioactive residues, aliquots of straw and ground grain were extracted twice with methanol. The insoluble fraction was filtered and refluxed with 5% (NH4)2CO3 in CH3OH/H2O. The methanol extracts were combined and concentrated. The (NH4)2CO3 extract was also concentrated by gently boiling on a hot plate. Essentially no activity (<0.5%) was extracted from the grain by methanol but about 18% was found in the methanol straw extracts. The (NH4)2CO3/H2O/MeOH removed between 15 and 20% of the residual activity from both fractions. No intact DPX-4189, 2-chloro- benzene sulfonamide or 2-amino-4-methoxy-6-methyl-1,3,5-triazine was detected (TLC) in the concentrated extracts. These latter two compounds were the major decomposition products of hydrolysis and photodegradation. The nature of the polar materials in the extracts could not be determined due to low levels present.

In another study field grown wheat planted in April was treated at 1 oz act/A (1x the proposed max. rate of application) when the seedlings were 8-10" tall. Both 14C-phenyl labeled DPX-4189 and 14C-triazine labeled DPX-4189 were used. The wheat was harvested during the third week of July. The mature wheat was separated into grain and straw and analyzed for total 14C radioactivity using the methods described for the wheat grown in the greenhouse. The radioactive residue in mature grain was found to be 0.008 and 0.016 ppm, respectively, calculated as intact DPX-4189. Corresponding residues in dry straw were 0.036 and 0.053 ppm. Extraction results were similar to those found for greenhouse grown wheat. Less than 0.5% of radioactivity was removed by methanol extraction from wheat grain but about 20-22% of 14C-residues were extracted from straw using the same solvent. (NH4)2CO3 in H2O/CH3OH removed an additional 14-34% of radioactivity from both grain and straw samples. No intact DPX-4189, 2-chlorobenzene-sulfonamide or 2-amino-4-methoxy-6-methyl-1,3,5-triazine were present in any of the extracts. In addition, pure lignin and glucosazone were isolated from the extracted straw samples. About 55.7% and 4.2% of the radioactivity from the phenyl labeled straw sample was isolated as lignin and glucosazone, respectively. Corresponding levels for the triazine label treated sample were 23.9% in the lignin and 11.7% in the glucosazone.
In another study leaves of young wheat plants were treated with 14C-DPX-4189 at 0.3-3 oz/A. After 24 hours the treated leaves were washed with acetone and extracted with 80% acetone. HPLC-MS and NMR were used to characterize the residue. The major radioactive component in the 24 hr leaf extracts was Metabolite A (see attachment). Small amounts of DPX-4189, the acid hydrolysis products of DPX-4189 and Metabolite A were also present.

Since total 14C residues in the wheat grain treated at rates exceeding the proposed application rate were <0.02 ppm and since the proposed use includes restrictions against feeding of treated forage or hay to livestock, we consider the nature of residue to be adequately delineated for the purpose of this experimental use permit. The regulation will be in terms of the parent compound only. However, for a permanent tolerance additional metabolism studies will be required. In particular, the nature of the residue in the straw should be elucidated.

In Animals

Two rats were pre-conditioned for 3 weeks on a diet containing 2,500 ppm DPX-4189. At the end of the three week period the rats were dosed orally with 50 microcuries 14C-CDPX 4189. Subsequently, the rats were maintained on water and diet supplemented with 2,500 ppm DPX as during the pre-conditioning period. Most (85.9%) of 14C-DPX-4189 was excreted unchanged in the urine during the 72 hrs following administration of the radiolabeled compound. The hydrolysis products of DPX-4189 were also isolated in the urine and were identified by mass spectrometry as 2-chlorobenzenesulfonamide (5.1%) and 2-amino-4-methoxy-6-methyl-1,3,5-triazine. Small amounts of intact DPX-4189 (identified by TLC) were also excreted via feces. Less than 1% of the radioactive dose was retained in the tissues and carcass. Concentrations ranged from 0.02 ppm in fat to 0.12 ppm in kidney and 0.18 ppm in the carcass.

The only feed items of concern are wheat and barley grain. Since no detectable residues of DPX-4189 are expected in grains from the proposed use, we consider the nature of the residue in animals to be adequately delineated for the purpose of this experimental use permit.

Analytical Method

To determine DPX-4189, wheat plants are extracted with ethyl acetate and filtered. The ethyl acetate solution is evaporated after addition of 10% (NH4)2 SO4 in 0.1M NaOH. The aqueous layer is then cleaned up in a separatory funnel with CHCl3, acidified with HCl and the residue is then partitioned into CHCl3. The CHCl3 extracts are then concentrated and extracted with 10% (NH4)2 SO4 in 0.1M NaOH. The aqueous phase is acidified and extracted with CH2Cl2. Residues of DPX-4189 are quantitated by HPLC. The above method was also used to obtain some of the data for barley, although a variation of the
method, discussed below, is considered to be more appropriate for
detection of residues of DPX-4189 in barley.

Control values were all <0.01 ppm for wheat grain and <0.05 ppm for straw.
Average recoveries from wheat grain were 59-60% at fortification levels of
0.01, 0.02, 0.04 and 0.06 ppm. Recoveries from the straw ranged from
60-80% at fortification levels of 0.05 ppm, 0.10 ppm and 0.30 ppm.
Control values from green forage were <0.05 ppm. No recoveries are
reported for green forage.

A variation of the above method was used to determine residues in barley
grain and straw. The principal modification involves the use of the
Na2HPO4/NaOH pH 10 buffer following the initial ethyl acetate
extraction. Control values were all <0.01 ppm for barley grain and <0.05
ppm for the straw. Recoveries ranged from 64-100% for barley grain
fortified at 0.01, 0.02 and 0.04 ppm and 65-86% for the straw fortified at
0.10-0.20 ppm. This compares with recoveries of 56-100% from barley grain
using the original method.

We conclude that there are adequate methods available for enforcement of
the proposed temporary tolerances in terms of the parent compound. If the
metabolism studies required for a permanent tolerance indicate the
presence of metabolites of DPX-4189 in wheat and barley plants which are
of toxicological concern, development of analytical methods for these
metabolites will be necessary.

Residue Data

Wheat

Residue data reflect 14 studies conducted in 7 states (NE, WY, KS, DE, SD, NM, OR). Wheat received a single application at rates ranging from 1
oz-32 oz/A (up to 32x the maximum proposed rate). PHI's ranged from
50-257 days with most samples harvested within 3 months of treatment. No
detectable residues of DPX-4189 were found in any grain (<0.01 ppm), green
forage (< 0.05 ppm) or straw (<0.05 ppm) samples.

Barley

Residue data reflect 4 studies conducted in 4 states (CA, MN, ND, WA). Treatments were made at rates ranging from 0.5-4 oz act/A (up to 5x the
max. proposed rate). PHI's ranged from 61-105 days. No detectable
residues, <0.01 ppm and <0.05 ppm, respectively, were found in any grain
or straw samples.
We conclude that residues of DPX-4189, per se, are not likely to exceed the proposed tolerance of 0.05 ppm in wheat and barley grain.

Since no detectable residues of DPX-4189, per se, were found in the grain of wheat and barley in any of the above studies and since total 14C-residues were <0.01 ppm in the grain from treatments with radiolabeled DPX-4189 at twice the proposed application rate, residues in milled grain are also expected to be non-detectable. Therefore, food additive tolerances are not needed.

Meat, Milk, Poultry and Eggs

The only feed items of concern are wheat and barley grain. Since no detectable residues of DPX-4189 are expected in the grains from the proposed use, there will be no problem with secondary residues in meat, milk, poultry or eggs.

If wheat or barley straw is found to contain metabolites of DPX-4189 which are of toxicological concern, large animal (ruminant) metabolism/feeding studies will be needed for a permanent tolerance.

cc: Reading file
Circu
Reviewer
FDA
PPP No.
TOX
EEB
EFB
Randy Watts


Attachment
\[ \text{DPX-4169} \]

\[
\begin{array}{c}
\text{Cl} \\
\text{SO}_2\text{NH-C-NH} \\
\text{N} \\
\text{CH}_3 \\
\text{OCH}_3
\end{array}
\]

\[ \sigma\text{-Chlorophenylsulfonamide} \]

\[
\begin{array}{c}
\text{Cl} \\
\text{SO}_2\text{NH}_2
\end{array}
\]

\[ 2\text{-Amino-4-methoxy-6-methyl-1,3,5-triazine} \]

\[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{N} \\
\text{CH}_3 \\
\text{OCH}_3
\end{array}
\]

\[ \text{Metabolite A} \]

\[
\begin{array}{c}
\text{Cl} \\
\text{SO}_2\text{NH-C-NH} \\
\text{N} \\
\text{CH}_3 \\
\text{OCH}_3
\end{array}
\]

\[ \text{A-1} \]