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Reviewer

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY AUG 4 1977

AUG 4 1977

SUBJECT: Request for a tolerance of 1.0 ppm of α-Naphthalene acetic acid (αNAA) in/on citrus fruits. DATE:

FROM: Dr. Chan, S.L.
Toxicology Branch

Sin-Lam Chan
B for OEP 8/4/77

TO: Mr. Fletcher, C.
Special Registration Section

Petition No. 7E1956
IR-4 Project
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Recommendations:

Chemistry Branch considerations permitting, we recommend the establishment of the petitioned tolerance of 1.0 ppm of αNAA and metabolites in/on citrus fruits.

We request that a teratology study be submitted within a reasonable period of time.

EPA Form 1320-6 (Rev. 6-72)

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A. Established and pending tolerances.

Tolerances have been established, CFR 40, 180.155 for:

1.0 ppm in/on apples, pears, quinces.
0.1 ppm in/on olives.
0.05 ppm in/on pineapples.

B. Referenced and related Petitions:

No new toxicological data are submitted for the current petition. The related petitions are 8E0663, 1E1094 and 1E1099. A summary of previously accepted toxicological studies is presented below:

1. Dr. Whitmore, G.E., on 8E0663 (12/22/67).

   a) 90-day rat feeding NEL = 100 mg/kg/day (ΑNAA).
   b) 90-day dog feeding NEL = 10 mg/kg/day (ΑNAA).
   c) 3-generation mouse reproduction study: no effect on reproductive performance to 600 ppm or 86 mg/kg (ΑNAA-O-CH_3).
   d) Life-time mouse feeding: no effect on life-span to 600 ppm (ΑNAA-O-CH_3).

2. Dr. Williams, C.H., on 1E1094 (5/19/71).

   a) Rat acute oral LD_{50} = 1.0 gm/kg (ΑNAA).
   b) 2-year rat feeding NEL = 2500 ppm (ΑNAA-O-CH_3).

3. Mr. Ritter, D.L., on 1E1099 (12/25/72).

   The possible toxicity arising from the impurities and plant metabolites was cleared.

   It is noted that in some studies, the methyl ester of ΑNAA was used instead of the salt. This is acceptable for 2 main reasons:

   a) ΑNAA is the principle metabolite of the methyl ester.
   b) Even though the exact amount of ΑNAA arising from its methyl ester is not known, the toxicity of both compounds are similarly low.

C. Studies presented (1E1099) but not previously reviewed.

1. Rat metabolism of αNAA-1-^{14}C, J. Agr. Food Chem., 14, 532 ('66).

Protocol: Single oral doses of 0.1, 1.0, 100 and 250 mg of αNAA-1-^{14}C were given to male rats. Radioactivity was monitored daily in the urine and feces and every 2 hrs. in the bile.

Results: The total radio-label excreted in 3 days was:

In urine = 71-90%
In feces = 3-20%
In bile = 4-21%, 2-6 hrs.

The 2 major metabolites (70-93%) in urine were naphthaceturic and naphthacetylglucosiduronic acids.

For the lower doses, the excretion in urine and feces in 24 hr. was approximately 90%.

Evaluation: αNAA and metabolites are well excreted in the urine and feces.

Classification: Core minimum.

D. 1. ADI estimation.

a) 90-day rat feeding NEL = 100 mg/kg/day.
b) 90-day dog feeding NEL = 10 mg/kg/day.
c) 2-year rat feeding NEL = 2500 ppm, or 125 mg/kg (αNAA-O-CH_3).
d) 3-generation mouse reproduction and life time feeding NEL = 86 mg/kg (αNAA-O-CH_3).

Since the methyl ester of naphthalene acetic acid was used in the long-term feeding and reproductive studies and the petition is for a tolerance of the free acid, a conservative estimate of the amount of the major metabolite, the free acid (αNAA) arising from the ester may be in the order of 1/10 of the parent compound. The estimated amount of αNAA is then used for the calculation of the ADI which may be revised accordingly when NELs for the free acid from long-term studies should become available.

Since the 2-yr. rat feeding NEL = 125 mg/kg/day, for the methyl ester.

The projected NEL for αNAA = 12.5 mg/kg/day.

Assuming then the usual factor of 100, the ADI may be estimated as:

ADI = 0.125 mg/kg/day.

The estimated MPI for a 60 kg person is:

MPI = 7.50 mg/person/day.

2. Exposure from established tolerances

	tolerance (ppm)	food intake (gm)	exposure mg/day
apples, pears, quinces	1.0	≈45.0	0.04500
olives	0.1	≈ 2.5	0.00025
pineapples	0.5	≈ 5.73	0.00030

total exposure = 0.0455 mg/day

3. Exposure from currently petitioned tolerance.

Exposure = 1.0 X 0.048 mg/person/day;

= 0.048 mg/person/day

(citrus fruits intake approximated at 48 gm per day).

4. Comparison of MPI to exposures from established and currently petitioned tolerances.

MPI/total exposure = 7.5/0.094

≈80

i.e. the exposure to αNAA and metabolites from the established and currently petitioned tolerances is approximately 1/80 of the estimated MPI.

E. Conclusion:

Tolerances of 0.05-1.0 ppm have been established for αNAA and metabolites to be in/on pineapples, olives, apples, pears and quinces. Previous and current reviews have found αNAA to be of a low order of toxicity in acute, subacute and chronic studies. The MPI may be estimated from these studies to be 7.50 mg/person/day. The exposure to αNAA and metabolites from the established and currently petitioned tolerances is a fraction (≈1/80) of the MPI.

Subject to chemistry considerations, we recommend on the establishment of the petitioned tolerance. However, according to current requirements, a teratology study is lacking and should be submitted within a reasonable period of time.

F. References:

1. rat acute oral LD_{50}: Toxic Substance List, 1975;
2. 90-day rat feeding: FDA files;
3. 90-day dog feeding: FDA files;
4. 3-generation mouse reproduction; and,
5. life-time mouse feeding: Finch, F., and Hartzell, A., (1945) Boyce Tomp. Inst. for Pl. Res. Vol. 14, P. 69;
6. 2-year rat feeding: FDA files.