Glyphosate / Tox

TOX R 002666 5803 (16)

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

Releasable

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM APR 15 1983

TO: Hoyt Jamerson (43)
Registration Division (TS-767)

THRU: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Increase Glyphosate (Roundup®) tolerance on curcubits
PP#3E2845; EPA Reg.#524-308; ~~CASWELL#661A~~

Recommendations:

a) This request to increase the tolerance on curcubits from 0.1 to 0.5 ppm can be toxicologically supported.

b) Chronic (and subchronic) oral toxicity data in a non-rodent species and an oncogenic study in a second species are data gaps.

Review:

1. Action Requested: This petition requests an increase in the tolerance from 0.1 ppm to 0.5 ppm for the combined residues of the herbicide glyphosate (N-phosphonomethyl glycine) and its metabolite, aminomethylphosphonic acid, in or on the raw agricultural commodities in the crop group curcubits, including Balsam pear, Chinese waxgourd, citron melon; cucumber; gherkin, edible gourds; melons (includes cantoloupe, casaba melon, Crenshaw melon, honeydew melon, honeyballs, mango melon, muskmelon, Persian melon); pumpkin; squash, summer; squash, winter; and watermelon, including hybrids.

2. The formulation to be used will be Roundup® (Mon 2139). Inerts are cleared under 180.1001.

3. Toxicological Studies:

No new data were submitted. Permission to EPA personnel to refer to Monsanto's files on Roundup® in support of this request was contained in a letter in the petition to the petitioner, IR-4 Project.

Studies supporting this action are listed in a previous review for glyphosate (memo dated 9-3-82 from Teeters to Taylor); since then the two IBT subchronic oral toxicity studies (#B-1020, rat and #B-1021, dog) and the reproduction study (IBT#B-566, rat) mentioned in the referenced memo have been evaluated and declared invalid.

Data gaps for glyphosate are a chronic (and subchronic) toxicity study in a non-rodent species and an oncogenic study in a second species.

4. Capen review of thyroid slides of female rats from a lifetime feeding study using glyphosate (re: memo from Dykstra to Taylor dated 2-10-83).

Relative to the Capen review, Dr. Kasza presented the following evaluation and conclusions; "Dr. Charles C. Capen, D.V.M., Ph.D.; Diplomate, American College of Veterinary Pathologists, has completed his investigation and basically he confirmed the diagnoses of the sponsor's pathologist; the tabulated results of Dr. Capen's investigation is shown below.

HISTOPATHOLOGIC EVALUATION OF THYROID GLANDS
FROM FEMALE SPRAGUE-DAWLEY (C/D) RATS
LIFETIME FEEDING OF GLYPHOSATE

Thyroid Lesion*	Control (n=47)	Low Dose (n=49)	Medium Dose (n=50)	High Dose (n=47)
C-Cell Hyperplasia (Nodular and/or Diffuse	19 (40%)	26 (53%)	25 (50%)	18 (38%)
C-Cell Adenoma	5 (11%)	3 (6%)	7** (14%)	3 (6%)
C-Cell Carcinoma	1 (2%)	0 (%)	1 (2%)	5*** (11%)

(n=) Number of thyroids available for microscopic evaluation.

*Diagnostic criteria used for thyroid C-cell lesions are given below.

**One previously diagnosed C-cell carcinoma (81-1168/603) was interpreted to be a C-cell adenoma according to criteria below.

***One previously diagnosed C-cell adenoma (81-1447/822) was interpreted to be multinodular chief cell hyperplasia of parathyroid gland; one C-cell carcinoma (81-1445/820) was interpreted to be a C-cell adenoma; one C-cell carcinoma (81-1454/824) was interpreted to be a C-cell adenoma; one C-cell adenoma (81-1231/828) was interpreted to be a C-cell carinoma according to criteria below.

The following are diagnostic criteria used for the interpretation of thyroid C-cell lesions in the rat:

1. C-(parafollicular) cell hyperplasia: A nodular and/or diffuse increase of C-cells between thyroid follicles and/or within the follicular basement membrane. The C-cells appear normal with an abundant, lightly eosinophilic, granular cytoplasm and a round-to-oval nucleus with finely stippled chromatin. Cell boundaries often are indistinct. Solid accumulations of C-cells are less than the size of a colloid-distended follicle. C-cells (1-2 cell layers thick) within the basement membrane may compress individual thyroid follicles.

2. C-(parafollicular) cell adenoma: Discrete, expansive mass or nodule of C-cells larger than a colloid-distended thyroid follicle. Adenomas are well-circumscribed or partially encapsulated from adjacent follicles that often are compressed to varying degrees. C-cells have an abundant cytoplasmic area that stains lightly eosinophilic and a round-to-oval nucleus with finely stippled chromatin. C-cells may be subdivided by fine connective tissue septae and capillaries into small clusters.

3. C-(parafollicular) cell carcinoma: Extensive proliferation of C-cells with enlargement of one or both thyroid lobes. There is evidence of intrathyroid and/or capsular invasion by the proliferating C-cells, often with areas of hemorrhage and necrosis within the neoplasm. The malignant C-cells often are more pleomorphic (cuboidal, oval, spindle-shaped) than with the benign proliferative lesions and have indistinct boundaries of the lightly eosinophilic cytoplasmic area. Mitotic figures may be numerous in the more anaplastic carcinomas.

Dr. Kasza continued, "We concluded from his review that some tumor diagnoses were changed mainly from malignant to benign. This indicated that the interpretation of benign and malignant neoplasms in the thyroid of rats sometimes varies according to individual pathologists.

Furthermore, a group of pathologists recently initiated a simplified method* to establish oncogenicity related to chemicals. Although this system has not yet received general acceptance, many highly competant pathologists agree with it. This system advocates grouping of neoplasms to determine the incidence in final analysis. The grouping of neoplasms took place on the consideration of their histogenetic origin. According to this recommendation the C-cell adenomas and C-cell carcinomas in rats should be combined in order to establish oncogenicity. This recommendation was based on findings in Fisher 344 rats; however, we have no reason to believe that diagnostic criteria would be any different for the strain (Sprague-Dawley) used in the glyphosate study. We agree with the recommendation of NTP. In addition, we also consider that the differentiation between benign and malignant C-cell tumors can somewhat differ based on varying criteria of individual pathologists.

*Working Paper entitled "Guidelines for Combining Benign and Malignant Neoplasms As An Aid In Determining Evidence of Carcinogenicity (Attachment 8) discussed at the National Toxicology Program, (NTP) Board of Scientific Counselors' Meeting, September 23 and 24, 1982.

Considering the above-mentioned two facts (Dr. Capen's diagnoses and the National Toxicology Program recommendation) we feel that we should combine thyroid benign and malignant C-cell tumors in order to evaluate the oncogenic potential of glyphosate in this rat lifetime study. When the combined incidence is compared there are no statistically significant differences between control (6/47) and test groups (3/49, 8/50 and 8/47)."

5. Several tolerances have been established under 40 CFR 180.364; for instance, leafy vegetables, root crops vegetables and seed and pod vegetables each have tolerances of 0.2 ppm.

6. Evaluation of ADI:

Based on a NOEL of 10 mg/kg/day in the reproduction study and using a safety factor of 100, the ADI is 0.1 mg/kg/day (10 mg/kg/day x $\frac{1}{100}$ = 0.1 mg/kg/day).

The MPI for a 60 kg person is 6 mg/day.

7. Total published and unpublished, but Toxicology Branch approved, tolerances utilize 23.73% of the ADI. All tolerances, including the one in this action, utilize 24.01% of the ADI and the TMRC is 1.4408 mg/day based on a 1.5 kg diet. This action increases the TMRC by 0.0170 mg/day, an increase of only 1.19%.

8. No regulatory actions are pending against the pesticide and no RPAR criteria have been exceeded.

9. Other relevant considerations:

Concentrations of 0.2-0.4 ppm of N-nitroso-glyphosate (NNG) are present in the formulated product (memo of 12-2-77 from Residue Chemistry Branch, PP#7F1971/FAP#7H5168) and there are three IBT studies with NNG which are yet to be evaluated (2-year orals in rat and dog and a rat reproduction). No detectable residues of NNG were found in soybean grain, forage and hay or in cottonseed using an analytical method sensitive to 0.02 ppm. Similar results would be expected with this use on curcubits, particularly since the herbicide is not to be applied directly to the plants in this crop group. No problem of serious toxicological concern is anticipated.

10. Conclusion:

a) This request to increase the tolerance on curcubits from 0.1 to 0.5 ppm can be toxicologically supported.

b) Chronic (and subchronic) oral toxicity data in a non-rodent species and an oncogenic study in a second species are data gaps.

Laurence D. Chitlik for 4/5/83

Winnie Teeters, Ph.D.
Review Section V
Toxicology Branch/HED (TS-769)

I concur with the interpretation of thyroid neoplasm incidence discussed in Item 4 above.

Louis Kasza

Louis Kasza, Pathologist
Toxicology Branch/HED (TS-769)

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CFR 180.364 Glyphosate Roundup 3/29/83

File last updated 3/16/83

ACCEPTABLE DAILY INTAKE DATA

RAT, Older mg/kg	NOEL ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
10.000	200.00	100	0.1000	6.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Grain Crops(64)	0.100	13.79	0.02069
Avocados(6)	0.200	0.03	0.00009
Citrus Fruits(33)	0.200	3.81	0.01144
Coffee(36)	1.000	0.75	0.01119
Grapes, inc raisins(66)	0.100	0.49	0.00074
Leafy Vegetables(80)	0.200	2.76	0.00828
Nuts(101)	0.200	0.10	0.00031
Pome Fruits(126)	0.200	2.79	0.00837
Root Crop Veg(138)	0.200	11.00	0.03299
Seed&Pod Veg(143)	0.200	3.66	0.01098
Palm Oil(202)	0.100	0.03	0.00005
Pistachio nuts(210)	0.200	0.03	0.00009
Asparagus(5)	0.200	0.14	0.00043
Bananas(7)	0.200	1.42	0.00426
Olives(104)	0.100	0.06	0.00009
Stone Fruits(151)	0.200	1.25	0.00374
Sugar, cane&beet(154)	2.000	3.64	0.10915
Molasses(96)	20.000	0.03	0.00920
Cranberries(44)	0.200	0.03	0.00009
Cottonseed (oil)(41)	15.000	0.15	0.03375
Kidney(203)	0.500	0.03	0.00023
Liver(211)	0.500	0.03	0.00023
Peanuts(115)	0.100	0.36	0.00054
Guava(184)	0.200	0.03	0.00009
Papayas(109)	0.200	0.03	0.00009
Mangoes(88)	0.200	0.03	0.00009
Soybeans (oil)(148)	6.000	0.92	0.08263
Pineapple(123)	0.100	0.30	0.00044
Fish, shellfish(59)	0.250	1.08	0.00406
Cucurbits(49)	0.100	2.84	0.00426
Fruiting Vegetables(60)	0.100	2.99	0.00449
Small Fruit, berries(146)	0.100	0.83	0.00124
Hops(73)	0.100	0.03	0.00005
Potable Water(198)	0.500	133.33	1.00000

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.3643 mg/day(1.5kg)	22.74

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Unpublished, Tox Approved 2F2680, 2G2686, 1H5310

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(148)	4.000	0.92	0.05509
Tea(162)	4.000	0.07	0.00429
Coconut(35)	0.100	0.03	0.00005

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.4238 mg/day(1.5)	23.73

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Current Action 3E2845

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Cucurbits(49)	0.400	2.84	0.01705

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.4408 mg/day(1.5kg)	24.01

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