

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

✓ 661A

DATE: March 6, 1978

Petition 89 2032

SUBJECT: 524-EUP-43. ROUNDUP. Glyphosate. Monsanto Company, St. Louis, Missouri.

FROM: Roland A. Gessert, D.V.M.
Toxicology Branch

TO: Ms. Libby Zink, Special Registration Section, Room 315(d)

Roundup contains technical N-phosphonomethylglycine. The technical product contains approximately 0.2 - 0.4 ppm of the impurity N-nitrosoglyphosate. The EUP is sought for experimental use in sugar beets and potatoes. Temporary tolerances are proposed for the combined residues of the herbicide and its soil metabolite aminomethylphosphonic acid in or on the raw agricultural commodities, as follows:

Sugar beets (roots)	0.2 ppm
Sugar beets (tops)	0.2 ppm
Potatoes	0.2 ppm
Liver & kidney of cattle, goats, hogs, horses, poultry, & sheep	0.1 ppm

Toxicity data on the technical compound and on the formulation are furnished by reference, and are not provided physically with this submission. Therefore, this review is based on previous reviews in the files for general toxicology.

Data submitted with this request demonstrate:

1. No detectable residue (less than 0.05 ppm) of glyphosate or its soil metabolite aminomethylphosphonic acid are present in or on sugar beets, sugar beet tops, or potato tubers grown on soil treated with twice the maximum recommended level of the herbicide.
2. Soil application to sugar beets results in a very low uptake into the plants (less than 0.04%) in 8 weeks.

In previous reviews by Dr. Mary Quaise it was noted that Chemistry Branch found 0.2 - 0.4 ppm N-nitrosoglyphosate in the Roundup formulation. In view of this low level of the nitroso compound in the formulation, the insignificantly low uptake of the glyphosate into the plant, and the absence of residue in the crop, Toxicology Branch considers any quantity of N-nitrosoglyphosate which may occur in foods to be not toxicologically significant.

In the previous reviews questions or criticisms were raised with certain studies, to wit:

- A. In the Ames-type in vitro test for mutagenicity of N-nitrosoglyphosate, 1) what are the actual amounts of the nitroso compound and of positive control chemicals (which are expressed as "microliters") used in the test, or per plate?

- A. 2) Was an adequate quantity of N-nitrosoglyphosate tested so that, even if it were of considerably less mutagenic potency than the positive control chemicals used, it could have yielded a positive result?
- B. In the mouse dominant-lethal mutagenicity test on N-nitrosoglyphosate (conducted by Industrial Bio-Test) the very low intraperitoneal doses of the nitrosamine used (5 & 10 mg/kg) relative to the rat oral LD₅₀ of the N-nitrosoglyphosate (5000 - 7000 mg/kg) are questioned.
- C. The teratology study on N-nitrosoglyphosate in the rabbit conducted by Industrial Bio-Test, if repeated, should use larger test doses, some of which are demonstrated to be toxic to the maternal rabbit. Also, at least 3 dose levels and a positive control should be used.

Based on data submitted and previous reviews the EUP may be granted and the temporary tolerances established as requested for use of Roundup on sugar beets and potatoes. However, prior to registration for these uses, the questions and criticisms in previous reviews should be addressed, and the confidential statement of formula should be furnished to Toxicology Branch for review.

Roland A. Gessert
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Toxicology Branch

For GCEW 3/8/78

The following, by reference, is a complete list of all toxicology completed for the registration of Roundup.

A. Acute Studies

	<u>Test Species</u>	<u>Test Number</u>	<u>EPA Accession Number</u>	<u>Reference Report</u>
Technical Glyphosate (CP 67573)				
1. Acute Oral	Rat	Y-70-90	94176	Section C, Part A
LD ₅₀	Rabbit	BTL-72-109	94176	Section C, Part B
2. Acute Dermal	Rabbit	Y-70-90	94176	Section C, Part B
MLD				
3. Skin Irritation	Rabbit	Y-70-90	94176	Section C, Part B
4. Eye Irritation	Rabbit	Y-70-90	94176	Section C, Part B
5. Subcutaneous	Rat	Y-51-151	94683	Section C, Part R
LD ₅₀				
6. Intraperitoneal	Rat	Y-73-112	94683	Section C, Part T

Roundup Formulation
(MON-2139)

1. Acute Oral	Rat	Y-72-160A	94176	Section C, Part D
LD ₅₀	Rat	Y-71-150	94176	Section C, Part C
2. Acute Dermal	Rabbit	Y-71-150	94176	Section C, Part C
MLD				
3. Skin Irritation	Rabbit	Y-71-150	94176	Section C, Part C
4. Eye Irritation	Rabbit	Y-71-150	94176	Section C, Part E
	Rabbit	Y-71-155	94176	Section C, Part E
	Rabbit	Y-74-74	50310	
	Rabbit	Y-75-150	94683	Section D, Part W
5. Acute Inhalation	Rat	BTL-74-166A	94683	Section C, Part S
	Rat	IBT-T2279	94161	Section C, Part O
6. Skin Patch test	Human	SH-72-19	94161	Section C, Part P

SECTION C Roundup Hazar to Humans and Domestic / mals
(continued)

	<u>Test Species</u>	<u>Test Number</u>	<u>EPA Accession Number</u>	<u>Reference Report</u>
Roundup Metabolite (CP 50435)				
1. Acute Oral LD ₅₀	Rat	Y-73-19	94161	Section C, Part Q
2. Eye Irrita- tion	Rabbit	Y-73-19	94161	Section C, Part Q
3. Skin Irrita- tion	Rabbit	Y-73-19	94161	Section C, Part Q
Roundup Surfactant (G3780A)				
1. Acute Oral LD ₅₀	Rabbit		93850	
2. Skin Irrita- tion	Rabbit		93850	
3. Eye Irrita- tion	Rabbit		93850	
4. Skin Patch test	Human		93850	
Glyphosate (Isopropylamine Salt) (CP 70139 or MON 0139)				
1. Acute Oral LD ₅₀	Rat Rat Rat	Y-75-149 Y-72-127 Y-72-328	95345 " "	Section C, Vol. 1 Section C " Section C "
2. Actue Dermal MLD	Rabbit Rabbit	Y-75-149 Y-72-127	" "	Section C " Section C "
3. Skin Irrita- tion	Rabbit Rabbit Rabbit	Y-75-149 Y-72-127 Y-74-56	" " 50310	Section C " Section C " 50310
4. Eye Irrita- tion	Rabbit Rabbit Rabbit	Y-75-149 Y-72-127 Y-74-56	95345 " 50310	Section C " Section C " 50310

SECTION C Roundup Hazards to Humans and Domestic Animals
(continued)

B. Sub-Acute, Chronic and Delayed Toxicology Studies

	<u>Test Species</u>	<u>Test Number</u>	<u>EPA Accession Number</u>	<u>Reference Report</u>
Roundup Formulation (MON-2139)				
1. 21-day Sub-acute Dermal	Rabbit	BTL-72-37	94176	Section C, Part F
Technical Glyphosate (CP 67573)				
1. 21-day Sub-acute Oral	Rabbit	BTL-74-7	94683	Section C, Part V
2. 90-day Sub-acute Oral	Rat	BTL-71-57	94161	Section C, Part H
	Beagle Dog	BTL-71-58	94176	Section C, Part G
3. Mutagenic	Mouse	BTL-71-35	94161	Section C, Part I
4. Carcinogenic (18 mo)	Mouse	BTL-71-37	94161	Section C, Part L
5. Teratogenic	Rabbit	BTL-71-36	94161	Section C, Part J
6. Reproduction	Rat	BTL-71-34	94161	Section C, Part K
7. 2 Yr Oral Chronic	Beagle Dog	BTL-71-33	94161	Section C, Part M
8. 2 Yr Oral Chronic	Rat	BTL-71-32	94161	Section C, Part N
9. CHE Inhibition	Rat	BTL-75-3	94683	Section C, Part U
10. Neurotoxicity Chicken		BTL-76-82	PP6G1862	Separate Bound Report
11. Analysis of Technical glyphosate used in long-term feeding studies.			96234	
12. Toxicology of N-nitrosoglyphosate			229785	Section C