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imagine

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201-14947

December 8, 2003

Mr. Michael O. Leavitt, Administrator
United States Environmental Protection Agency
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Administrator Leavitt:

Monsanto Company is pleased to submit the proposed test plan and robust summaries for the chemical glyphosate intermediate (GI), CAS# 5994-61-6. Monsanto Company understands this information will be posted on the Internet for comments for a period of 120 days, and comments may be forwarded to my attention at the company address for consideration.

Enclosed with this letter is a computer diskette containing the test plan and robust summaries in Adobe Acrobat (.pdf) format.

The HPV registration number for Monsanto Company is

Sincerely,

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Clyde L. Livingston
Chemical Regulatory Compliance
Monsanto Company

201-14947

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN FOR

GLYPHOSATE INTERMEDIATE

(CAS NO.: 5994-61-6)

PREPARED BY:

Monsanto Company

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December 8, 2003

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OVERVIEW

Monsanto Company hereby submits for review and public comment the test plan for glyphosate intermediate (GI) (CAS No. 5994-61-6) included by the High Production Volume (HPV) Challenge Program in conjunction with the United States Environmental Protection Agency (US EPA) and the chemical industry.

Monsanto Company is a major producer of agricultural pesticides regulated and registered in the United States by the US EPA in accordance with provisions of the Federal Insecticide Fungicide and Rodenticide Act (FIFRA). The herbicide glyphosate is the active ingredient in Roundup® branded products used worldwide for effective, non-selective weed control through a mode of action that is not present in insects, birds, fish, mammals and humans. During a final step in the well-controlled and carefully engineered manufacturing process of the glyphosate technical material, GI is converted to glyphosate by removal of a single N-carboxymethyl moiety in a manner that minimizes worker exposure to the chemical intermediate. The final glyphosate technical material has been thoroughly tested and characterized in risk assessment evaluations addressing the toxicological endpoints indicated in the Screening Information Data Set (SIDS). When glyphosate herbicides are used according to label directions, no unreasonable adverse effects to people, wildlife, and the environment are expected. Glyphosate is approved by the US EPA for use in several registered pesticide products.[1, 2, 3, 4, 5] With considerable similarity between GI and glyphosate in chemical structure, chemical properties and chemical degradation products, the similar conclusion about GI not posing unreasonable risks to human health or the environment can be reached.

In conjunction with existing data for glyphosate (a structural analog), the existing data available for GI is adequate to address the goals and objectives of the HPV Challenge Program without the need to conduct any new or additional testing.

JUSTIFICATION FOR THE USE OF SURROGATE AND ADDITIONAL DATA WITH GLYPHOSATE

HPV Challenge participants were directed in a letter from the US EPA dated October 14, 1999 to maximize the use of existing data together with the existing data of scientifically appropriate related chemicals in order to minimize additional animal testing. Structure-activity relationships, or SAR, could be used to reduce testing in at least three different ways. Among the suggested possibilities, SAR principles could be applied to a single chemical that is closely related to one or more better characterized chemicals ("analogs").[6] Monsanto Company therefore intends to satisfy the goals of the HPV Challenge Program for GI by providing existing data to address each SIDS endpoint where either adequate data already exists for GI itself, or adequate existing data is provided by glyphosate (an acceptable structural surrogate).

The chemical structures of GI and glyphosate are the same except that GI has two carboxymethyl moieties bonded to the amine nitrogen and glyphosate has only a single carboxymethyl moiety on that amine nitrogen. (See the structures provided in the substance information section of the Robust Summaries, attached).

Glyphosate is among the most studied and characterized chemicals in use today, and it is logical to incorporate the extensive information already available about the toxicology and ecotoxicology of glyphosate as a well-characterized chemical "analog" for GI because they are so closely related in structure, in chemical properties, and in environmental properties.[1, 2, 3, 4, 5]

Numerous environmental fate, toxicology and ecotoxicology studies have been conducted with glyphosate and formulations of glyphosate. Extensive reviews and evaluations of these studies have concluded that glyphosate is not genotoxic, not carcinogenic, and it does not have reproductive toxicity of concern. The US EPA has assigned a Reference Dose for oral chronic exposure of 2 mg/kg bw/day (sometimes stated as 1.75 mg/kg/day), and has determined that there is no acute endpoint of concern on which to base an acute reference dose. Glyphosate has been registered for

sale as the active ingredient in popular herbicide products for more than 25 years, and is one of the most widely used products for agriculture worldwide, with a documented record of effective use without posing any unreasonable health risk to humans under expected conditions of application. Since GI has such a closely related chemical structure to glyphosate, it also has very similar physical properties and degradation products as glyphosate. Toxicity testing of GI itself indicates that it is similar to glyphosate in producing results indicative of low toxicity. GI, in fact, is a low-level impurity (nominal 0.3%) in technical grade glyphosate.

The exclusive use of GI as the final intermediate in the controlled, carefully engineered manufacturing process of glyphosate, minimizes the potential exposure to both workers and the environment. Worker exposure during manufacturing operations is monitored and has been shown to be easily minimized through engineering controls, or when necessary, through employment of personal protective equipment. The greatest potential for human exposure would occur during bagging and shipping operations that may occur to transport GI between separate manufacturing locations. Based on the similarity of structure and properties, and the known toxicological properties of glyphosate, Monsanto Company believes that it can be concluded with reasonable certainty that the small potential for exposure to GI during transport relative to glyphosate manufacture will not result in unreasonable harm to humans or the environment.

In total, these data are believed to be adequate to fulfill the requirements of the HPV Challenge Program without the need to conduct any new or additional tests.

TEST PLAN SUMMARY

Glyphosate Intermediate CAS Registry Number: 5994-61-6	Data Available	Data Acceptable (Y/N)	Testing Required (Y/N)
PHYSICAL/CHEMICAL PROPERTIES			
Melting Point	Decomposes >200 C	Y	N
Boiling Point	Not distillable	Y	N
Vapor Pressure*	1.94×10^{-7} mm Hg @ 45C	Y	N
Partition Coefficient	K_{ow} <1.0	Y	N
Water Solubility	0.7 g/100 mL @ 25 C 2.4 g/100 mL @ 70 C 5.4 g/100 mL @ 100 C	Y	N
ENVIRONMENTAL FATE			
Photolysis*	Stable; no significant photodegradation	Y	N
Stability in Water (Hydrolysis)*	Not hydrolyzed in sterile water	Y	N
Biodegradation	Degraded by microorganisms	Y	N
Transport between Environmental Compartments	Strong adsorption to soils; not likely to move through soil to reach groundwater	Y	N
ECOTOXICITY**			
Acute Toxicity to Fish	96-hour LC_{50} rainbow trout: 75 mg/L, slightly toxic	Y	N
	96-hour LC_{50} bluegill sunfish: 75 mg/L, slightly toxic	Y	N
Acute Toxicity to Aquatic Invertebrates	48-hour EC_{50} *Daphnia magna*: 700 mg/L, practically nontoxic	Y	N
Toxicity to Aquatic Plants	96-hour EC_{50} marine algae (*Skeletonema*): 140 mg/L, practically nontoxic	Y	N
MAMMALIAN TOXICITY**			
Acute Toxicity	Inhalation, rat 4-hour LC_{50}: >6.1 mg/L, practically nontoxic	Y	N
	Oral, rat LD_{50}: 2,200 mg/kg, slightly toxic	Y	N
	Dermal, rabbit LD_{50}: >5,000 mg/kg, practically nontoxic	Y	N
	Eye irritation, rabbit: severely irritating	Y	N
	Skin irritation, rabbit: nonirritating	Y	N
Repeated Dose Toxicity	4-week dermal, albino rat: no systemic toxicity	Y	N
Genetic Toxicity	Cell culture DNA repair assay: not genotoxic	Y	N
	Microbial and yeast assays: not mutagenic	Y	N
Reproductive Toxicity	Albino rat, repeated inhalation exposure NOEL: 9.6 mg/m^3 of air	Y	N
Developmental Toxicity	Rat teratology NOEL: 400 mg/kg/day	Y	N

* This endpoint is either completed or supported through the use of data on glyphosate used as a surrogate.
** Toxicity classification is based on US EPA guidance.

SIDS DATA SUMMARY

General Information: GI is a well-characterized substance used exclusively as a chemical intermediate in the manufacture of the herbicide glyphosate, the active ingredient present in Roundup® branded herbicides. The potential for any significant human exposure is primarily limited to a relatively small number of workers at the manufacturing facilities. Worker exposure is controlled, as needed, by engineering or through the use of personal protection equipment. Monitoring data of potential worker exposures has shown that all worker exposures have been below the limits established by company guidelines to protect workers against any possible hazards.

Physical/Chemical Properties: Data to assess the various physical/chemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) of GI were obtained from company reports that document the experimental results for each of these parameters with either GI or glyphosate as the chemical analog (vapor pressure). GI and glyphosate are similar amino acids and have similar physical properties with respect to decomposition upon heating without a defined boiling point, very soluble in water, and extremely low partition coefficient. In fact, the average value of the octanol/water partition coefficient (K_{ow}) for GI was 0.09 based on the amount of GI recovered from the aqueous layer. The vapor pressure for GI is also expected to be similar to the very low value measured for glyphosate.

Environmental Fate: Data to assess the environmental fate properties (photolysis, hydrolysis, biodegradation, and transport between environmental compartments) of GI were obtained from published articles as well as company reports. Studies with ^{14}C-radiolabeled glyphosate were conducted to establish that it is stable to photodegradation in both soil and sterile water, and established that it is not hydrolyzed in sterile water. Similar results would be expected for GI since the type of chemical bonds and functional groups in the two molecules are identical. However, microorganisms have been shown to readily degrade GI, and biotreatment studies have identified and characterized a microorganism that readily biodegrades GI from industrial activated sludges. To assess the transport of GI between environmental compartments, soil adsorption/desorption data using ^{14}C-radiolabeled GI demonstrated the strong adsorption to most soils with a high degree of binding. Similar to glyphosate, GI would not be found in air, and tight binding to most soil types means that it would be unlikely to leach or runoff significantly into ground or surface water. Because GI is an ionizable amino acid, it partitions strongly in favor of water rather than fat / oil / organic phases, and is not expected to bioconcentrate or accumulate in the food chain.

Ecotoxicity: Data to assess the ecotoxicity of GI to fish, aquatic invertebrates, and marine algae were obtained from company reports for studies conducted according to regulatory guidelines. The 96-hour LC_{50} values obtained for both rainbow trout and bluegill sunfish were 75 mg/L, and result in GI being classified as "slightly toxic" to fish. The *Daphnia* 48-hour EC_{50} (700 mg/L) and the *Skeletonema* 96-hour EC_{50} (140 mg/L) were higher than the fish endpoints, and result in GI being classified as "practically nontoxic" to aquatic invertebrates and marine algae. The potential for significant exposures of natural aqueous environments to GI is extremely unlikely, except for unusual conditions such as a major accidental release to the environment during transport. In the event of such a release, GI has been shown to be readily biodegraded by wastewater microorganisms, as previously noted.

Mammalian Toxicity: Data to assess the mammalian toxicity potential (acute, repeated dose, genetic, reproductive, and developmental) of GI were obtained from company reports on studies conducted according to international guidelines under Good Laboratory Practices (GLP). The LD_{50} for acute oral exposure in the albino rat to GI was 2,200 mg/kg, corresponding to US EPA pesticide

category III, slightly toxic. GI is considered to be practically nontoxic via both acute dermal and inhalation exposure. The acute dermal LD_{50} in rabbits was greater than 5,000 mg/kg, and the 4-hour acute inhalation LC_{50} in rats was greater than 6.1 mg/L. GI was found to be severely irritating to eyes, but nonirritating and nonsensitizing to skin. No systemic toxicity was noted in rats exposed to GI by either repeated dermal exposure or inhalation exposure. Results from a cell culture DNA repair assay and from a microbial mutagenic assay indicate that GI is not genotoxic and not mutagenic. No significant adverse effects were noted in studies of reproductive toxicity and developmental toxicity. These results for GI are similar to those obtained for glyphosate. Glyphosate has been more extensively studied (see the references in the Appendix).

In conclusion, the SIDS endpoints have been addressed in meeting the objectives of the HPV Challenge Program for GI without the need to conduct any new or additional testing. The robust summaries are provided with this test plan. Where appropriate, some endpoints have been completed or supplemented by a logical comparison to glyphosate as a model compound. The summarized data support the assessment that GI, especially in its exclusive role as a chemical intermediate for manufacturing use, poses no unreasonable risk of harm to workers, or to the general population and the environment.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The existing data for GI was reviewed for quality and acceptability according to the general guidance provided by the US EPA for meeting the SIDS requirements for each endpoint.[7, 8] Additional data existing for glyphosate, as a closely related chemical analog for GI, were reviewed and are provided to supplement or reinforce the GI data for some of the environmental fate and toxicological endpoints. Glyphosate experimental data taken from Monsanto Company reports have been accepted and used by the US EPA under guidelines established for the registration of pesticide products. The approach described by Klimisch *et al.* (1997) specifies four categories for classifying adequacy of data applied to the ecotoxicology and human health endpoint studies.[9]

1. Reliable without Restriction: GLP procedures followed, accepted testing guideline followed.
2. Reliable with Restrictions: Documented procedures, but vary slightly from testing guidelines.
3. Not Reliable: Unknown or unacceptable testing methods, test organisms, or route of exposure.
4. Not Assignable: Insufficient detail to assign a rating.

REFERENCES

1. Gary M. Williams, Robert Kroes, and Ian C. Munro. "Safety Evaluation and Risk Assessment of the Herbicide Roundup® and Its Active Ingredient, Glyphosate, for Humans," Regulatory Toxicology and Pharmacology, **31,** 117-165 (2000). Abstract available online at http://dx.doi.org/10.1006/rtph.1999.1371
2. "Summary of Human Risk Assessment and Safety Evaluation on Glyphosate (and Roundup® Herbicide)", Monsanto Company Backgrounder, November, 2001. Attached in the Appendix to this test plan for conveniently reviewing the reference.
3. "Summary of Ecotoxicological Risk Assessment for Roundup® Herbicide," Monsanto Company Backgrounder, November, 2001. Attached in the Appendix to this test plan for conveniently reviewing the reference.
4. "Glyphosate and Standard Toxicology Studies," Monsanto Company Backgrounder, September, 2002. Attached in the Appendix to this test plan for conveniently reviewing the reference.

5. "Glyphosate and Environmental Fate Studies," Monsanto Company Backgrounder, April, 2003. Attached in the Appendix to this test plan for conveniently reviewing the reference.
6. US EPA (1999). "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Challenge Program" OPPT, EPA.
7. US EPA (1999). "Determining the Adequacy of Existing Data" OPPT, EPA.
8. US EPA (1998). "Guidance for Meeting the SIDS Requirements (The SIDS Guide)" OPPT, EPA.
9. Klimisch, H.-J., Andreae, M., and Tillman, U. (1997). "A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data" Regul. Toxicol. Pharmacol. **25**: 1-5.

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ROBUST SUMMARIES

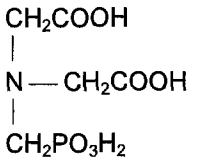
I. General Information

a. Substance Identification

CAS Registry Number: 5994-61-6

Chemical Name: Glycine, N-(carboxymethyl)-N-(phosphonomethyl)-

Structural Formula:



Other Names: Glyphosate Intermediate (GI)
N-(Phosphonomethyl)iminodiacetic acid (PIA)
MON 5735
CP 41820

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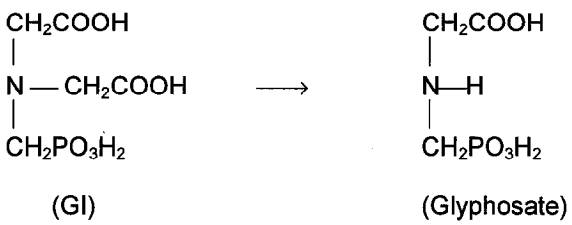
b. Substance Description

Chemical Formula:	C5H10NO7P
Molecular Weight:	M.W. = 227.1
Appearance:	Off-white solid
Odor:	No odor
Additional information:	
Density:	46.2 lb/cu ft (bulk density), GI (technical grade)
Particle size:	99% <30 mesh, GI (technical grade)
Flash point , (C.O.C):	None, >171 C, GI (technical grade)
Flammable limits:	Not combustible under normal conditions
Explosive properties:	Not explosive. No exotherms in the temperature range of 25 C to 400 C
Dissociation Constants:	$_pK_1$ = 2.00, $_pK_2$ = 2.25, $_pK_3$ = 5.57, $_pK_4$ = 10.76 (in 0.1 N KCl at 20 C)
Reactivity:	
Oxidizing properties:	Oxidized by $KMnO_4$
Chemical compatibility:	No reaction with H_2O, CO_2, Zn, Cu, $(NH_4)_3PO_4$
Polymerization hazards:	None
Instability conditions:	Contact with oxidizing agents in aqueous media; Not hazardous
Decomposition products:	Product – glyphosate (N-phosphonomethylglycine); Not hazardous Product – aminomethylphosphonic acid (AMPA); Not hazardous Product – hydroxymethylphosphonic acid (HMPA); Not hazardous

c. Substance Used as Chemical Intermediate for the Manufacture of Glyphosate

GI is used to manufacture glyphosate, the active ingredient in several Roundup® herbicide formulations. Glyphosate is produced by Monsanto Company at manufacturing sites within the United States of America located at Luling, Louisiana and at Muscatine, Iowa.



The sole use of GI is in the production of the herbicide glyphosate. The herbicide glyphosate is the active ingredient in Roundup® branded herbicide products used for effective, non-selective weed control. During a final step in the manufacturing process of glyphosate, the GI is converted to glyphosate by removal of a single N-carboxymethyl moiety in a manner that minimizes worker exposure to the chemical intermediate. The final glyphosate product has been thoroughly studied and characterized in risk assessment evaluations addressing toxicological endpoints identified by the SIDS endpoints. Glyphosate does not pose an unreasonable risk to human health or the environment, and glyphosate is approved by the US EPA for use in several registered pesticide products. (See the references and backgrounder information provided in the Appendix).

With considerable similarity in chemical structure and chemical properties, resulting in similar degradation products for GI and glyphosate, the similar conclusions about GI not posing an unreasonable risk to human health or the environment can be reached. Not only has the active ingredient glyphosate been studied in a battery of tests required by the US EPA under the provisions of FIFRA to evaluate the health and environmental risks associated with its use as a registered pesticide, but product formulations containing glyphosate as the active ingredient together with other inert ingredients and associated impurities must receive US EPA registration approval. GI can exist in small amounts (nominal 0.3% concentration) as an impurity in the approved glyphosate final technical product.

Although GI is only a chemical intermediate and not the final product, some GI produced at the Monsanto Company location at Luling, Louisiana, can be shipped to another Monsanto Company manufacturing plant at Muscatine, Iowa, or other similar non-Monsanto Company manufacturing sites. Shipment is done by truck or rail with the chemical contained in specially designed tanks called isotainers that greatly reduce or eliminate exposure to the chemical intermediate.

The potential for human exposure is greatest for the workers at the manufacturing facilities. Worker exposure to GI (particulate) is controlled

through the use of engineering controls where possible, and if other controls are not appropriate, through the use of personal protection equipment (PPE). The most common type of engineering control is local exhaust ventilation (LEV) and is used in places where the dry material is handled, to prevent dust inhalation. The most common type of PPE used is called respiratory protection which is in the form of a full, or half-face piece, tight-fitting respirator with high efficiency type filter cartridges. The only area in the GI production facility that requires the use of PPE for normal operations is the bagging area that handles the dry material. Some maintenance operations such as cleaning out dust collection systems (that connect to the LEV) also require the use of PPE. Normal operations that handle the wet material (known as Wet Cake) do not usually require engineering controls or PPE to control the exposure to GI.

Monitoring data of potential worker exposure to GI is available and completed routinely on a bi-annual schedule for normal operations, and assessments are made for maintenance operations and other non-routine operations. No federal guidelines or exposure limits have been specified for GI, however Monsanto Company has adopted an internal Industrial Hygiene (IH) Monsanto Workplace Exposure Guideline (MWPEG) of 0.5 mg/m^3 8-hour time weighted average (TWA) for exposure to GI based upon nasal irritation. The IH monitoring samples are collected using a calibrated air pump and filter to concentrate the sample followed by an HPLC Post-Column derivatization method to analyze for GI. A full-shift 8-hour sample normally results in a detection limit of about 0.15 mg/m^3. Worker exposure can vary considerably depending on the area, the type of GI (wet or dry) and the activity of the worker. The overall range in results from all monitoring at the production facility is <0.15 to 12 mg/m^3, where the highest value was obtained for a maintenance operation where filters were replaced on the dust collection system and workers were equipped with appropriate PPE. In every case where the exposure potential has exceeded the MWPEG of 0.5 mg/m^3, the workers have worn the appropriate PPE so that the theoretical range of exposures were actually reduced to <0.15 to 0.3 mg/m^3. With appropriate PPE when necessary, IH monitoring data has shown that all worker exposures are below the MWPEG.

II. Physical-Chemical Data

a. Melting Point

Test Substance:	GI (pure compound)
Result:	Decomposes at temperatures greater than 200 C 313 C (Calculated)
Method:	Testing procedure conformed closely to both OECD Guidelines for Testing of Chemicals (Section 1: Physical-Chemical Properties), and EPA requirements for U.S. premanufacturing notification.
Data Quality:	Data obtained from experimental measurements. Calculated data from Selected Values of Chemical Thermodynamic Properties, Circular 500 from the National Bureau of Standards, 1952, Washington, D.C.
References:	Monsanto Company (1999). Material Safety Data Sheet No. S00012764 (July 12, 1999). Hammond, J. L. "Australian Notification Base Testing Requirements for N-(Phosphonomethyl)iminodiacetic Acid (Glyphosate Intermediate) Part I: Physical/Chemical Data"; Monsanto Company Report No. MSL-7663 (1985). Eaton, David R. "Thermal Stability of Glyphosate Intermediate and Glyphosate"; Monsanto Company Report No. MSL-14479 (1996).
Remarks:	The thermal stability of both GI and glyphosate have been studied and are similar. Although both GI and glyphosate are very stable materials, at extreme temperatures above 150 C, both GI and glyphosate decompose accompanied by evolution of gases consisting mainly of water, carbon monoxide, carbon dioxide, and ammonia. Neither GI nor glyphosate displays a significant tendency to rapidly self heat.
Other:	

b. Boiling Point

Test Substance:	GI (pure compound)
Result:	Not distillable
Method:	
Data Quality:	Data obtained from experimental measurements.
References:	Hammond, J. L. "Australian Notification Base Testing Requirements for N-(Phosphonomethyl)iminodiacetic Acid (Glyphosate Intermediate) Part I: Physical/Chemical Data"; Monsanto Company Report No. MSL-7663 (1985).
Remarks:	
Other:	

c. Vapor Pressure

Test Substance:	Glyphosate (pure compound)
Result:	1.94×10^{-7} mm Hg at 45 C
Method:	Testing procedure conformed closely to both OECD Guidelines for Testing of Chemicals (Section 1: Physical-Chemical Properties), and EPA requirements for U.S. premanufacturing notification
Data Quality:	Data obtained from experimental measurements.
References:	Hammond, J. L. "Australian Notification Base Testing Requirements for N-(Phosphonomethyl)iminodiacetic Acid (Glyphosate Intermediate) Part I: Physical/Chemical Data"; Monsanto Company Report No. MSL-7663 (1985).
Remarks:	It is expected that GI has a similarly low vapor pressure.
Other:	

d. Partition Coefficient

Test Substance:	GI (pure compound)
Result:	n-octanol/water: <1.0
Method:	EPA Chemical Fate Test Guidelines, CG-1400, Report # EPA 560/6-82-003, August 1982 (USA).
Data Quality:	Data obtained from experimental measurements.
References:	Hammond, J. L. "Australian Notification Base Testing Requirements for N-(Phosphonomethyl)iminodiacetic Acid (Glyphosate Intermediate) Part I: Physical/Chemical Data"; Monsanto Company Report No. MSL-7663 (1985).
Remarks:	The octanol/water partition coefficient was determined to be significantly less than 1. The K_{ow} was estimated at pH values of 5, 7, and 9 by analyzing the aqueous layer by HPLC. The amount of GI not recovered in the aqueous layers was far below the detection limits for quantitation of GI in octanol. The average value of the K_{ow} was 0.09 based on the amount of GI found in the aqueous layer.
Other:	

e. Water Solubility

Test Substance:	GI (pure compound)
Results:	0.7 g/100 mL @ 25 C 2.4 g/100 mL @ 70 C 5.4 g/100 mL @ 100 C
Method:	Testing procedure conformed closely to both OECD Guidelines for Testing of Chemicals (Section 1: Physical-Chemical Properties), and EPA requirements for U.S. premanufacturing notification.
Data Quality:	Data obtained from experimental measurements.
References:	Monsanto Company (1999). Material Safety Data Sheet No. S00012764 (July 12, 1999). Hammond, J. L. "Australian Notification Base Testing Requirements for N-(Phosphonomethyl)iminodiacetic Acid (Glyphosate Intermediate) Part I: Physical/Chemical Data"; Monsanto Company Report No. MSL-7663 (1985). Standard Manufacturing Process for N-Phosphonomethyliminodiacetic Acid (Glyphosate Intermediate), Monsanto Agricultural Products Company, Fayetteville, North Carolina. Prepared by R. E. Byrd 10/19/82. Chrisope, D. R. "Solubility of Glyphosate Intermediate"; Monsanto Company Report No. MSL-15719 (1998).
Remarks:	NaCl and pH were significant factors affecting solubility of GI.
Other:	

III. Environmental Fate Endpoints

a. Photodegradation

Test Substance:	[^{14}C]Glyphosate (98.9% radiochemical purity)
Result:	There is minimal degradation of glyphosate in/on soil by natural sunlight.
Method:	US EPA Pesticide Assessment Guidelines, Subsection N-161-3 to fulfill the data requirements for soil photolysis.
Data Quality:	This is a well-documented US EPA guideline study conducted under GLP assurances.
References:	K. Shepler, and P.A. McGovern, "Photodegradation of [^{14}C]Glyphosate in/on Soil by Natural Sunlight," Monsanto Company Report No. MSL-9271, PTRL-153W, R.D. No. 972 (1989). Rueppel, M.L., Brightwell, B.B., Schaefer, J., and Marvel, J.T., "Metabolism and degradation of glyphosate in soil and water," J. Agric. Food Chem., **25**, 517-522 (1977).
Remarks:	The photoreactions of the herbicide [^{14}C]glyphosate under natural sunlight were examined on a sandy loam soil surface. The study was conducted at a typical field application rate of 4.0 lb/acre. The half-life of glyphosate, estimated based upon a linear extrapolation to the first order model, was 90.2 days (R=0.82) in sunlight and 96.3 days (R=0.86) in the dark. The primary degradates observed in both light exposed and dark control samples were aminomethylphosphonic acid (AMPA) and carbon dioxide. The tenacity with which glyphosate and AMPA bind to soil is widely recognized. As the study proceeded, extraction of radiocarbon from the sandy loam became increasingly difficult. Through exhaustive extraction of the soil samples, the radiocarbon bound to post-extraction solids was reduced to <10% of that applied. The average soil surface temperatures during the course of the study were 22.6 ± 0.2 C for the light exposed samples and 21.9 ± 0.2 C for the dark control samples.
Test Substance:	[^{14}C]Glyphosate (100.0% radiochemical purity)
Result:	Glyphosate is stable to photodegradation in aqueous solutions. Minimal photodegradation of [^{14}C]glyphosate was observed at pH 5, 7, or 9.
Method:	US EPA Pesticide Assessment Guidelines, Subsection N-161-2; Photodegradation in Water.
Data Quality:	This is a well-documented US EPA guideline study conducted under GLP assurances.
References:	Stephan Castle, Luis O. Ruzo, and Kathryn Shepler, "Degradation Study: Photodegradation of [^{14}C] Glyphosate in a Buffered Aqueous Solution at pH 5, 7 and 9 by Natural Sunlight," PRTL Report No. 233W-1, R.D. No. 1020 (1990).
Remarks:	[^{14}C]Glyphosate was exposed to natural sunlight in sterile pH 5, 7, and 9 aqueous buffers, concurrently with dark control samples. All samples were maintained in a water bath and the average temperature throughout the study period was 24.5 ± 0.7

Other:	C. The nominal test substance concentration was 0.9, 0.9, and 0.8 ppm for the pH 5, 7, and 9 buffer solutions, respectively. The pH 7 study was conducted with volatile trapping and consisted of a zero time and five additional samples taken over a 31-day period. The extrapolated half-life of degradation of glyphosate was 413 days in light exposed and 555 days in dark control samples. The correlation coefficients (R^2) for the linear regression calculations were poor (0.15 and 0.09 for the light and dark respectively) reflecting the minimal degradation which occurred during the 31-day study period. No unknown products were observed by HPLC analysis, organic volatiles represented less than 0.6% of applied radiocarbon, and 0.4% was trapped as CO_2. Material balance was good, averaging 97.1 ± 4.5% and 95.7 ± 4.7% for the light and dark samples, respectively. The comparative studies, conducted under the same conditions in pH 5 and 9 buffer solutions, consisted of time zero and 29-day samples in sealed containers without volatile trapping. Material balance averaged 101.0 ± 1.5% and 100.5 ± 0.5% for the light and dark samples in pH 5 buffer, and 100.8 ± 0.3% and 98.8 ± 0.6% in pH 9 buffer, respectively. Results of the HPLC analysis of these samples were consistent with the pH 7 study.

b. Stability in Water (Hydrolysis)

Test Substance:	Glyphosate (^{14}C-labeled pure compound)
Result:	There is no evidence of hydrolysis of glyphosate in sterile buffers at pH 3, 6, or 9. All samples analyzed showed the presence of glyphosate at the same concentration within experimental error of the HPLC analysis for the starting material.
Method:	Hydrolysis of ^{14}C-labeled glyphosate was determined in sterile buffers (pH 3.0, pH 6.0, and pH 9.0) at 25 ppm and 250 ppm. The sterile solutions were incubated in the dark at 5 degrees C and 35 degrees C for 32 days. Duplicate samples were analyzed at 0, 7, 14, 21 and 32 days for ^{14}C-labeled radioactivity remaining in solution and samples were analyzed chromatographically for the amount of glyphosate starting material that remained.
Data Quality:	Data obtained from experimental measurements.
References:	B.B. Brightwell, and J.M. Malik, "Solubility, Volatility, Adsorption and Partition Coefficients, Leaching and Aquatic Metabolism of MON 0573 and MON 0101," Monsanto Company Report No. MSL-0207, R.D. #181 (1978). Hammond, J. L. "Australian Notification Base Testing Requirements for N-(Phosphonomethyl)iminodiacetic Acid (Glyphosate Intermediate) Part I: Physical/Chemical Data"; Monsanto Company Report No. MSL-7663 (1985). G. Schwarzenbach, H. Ackermann, and P. Ruckstuhl, Helv. Chim. Acta., 32, 1175 (1949).
Remarks:	Slow biodegradation of glyphosate to AMPA occurs in natural waters of pH 4.23, pH 6.25, and pH 7.30. Based upon similar chemical structures, the same chemical functional groups, and the same chemical bond types, GI would also be resistant to hydrolysis in sterile water. GI is readily converted to glyphosate by other chemical processes.
Other:	

c. Biodegradation

Test Substance:	[^{14}C]GI (pure compound, >99% radiochemical pure [*carboxymethyl*-2-^{14}C]GI)
Result:	The stoichiometric conversion of GI to aminomethylphosphonic acid (AMPA) was observed in a laboratory sequencing batch reactor (SBR) containing activated sludge from a glyphosate-manufacturing facility and GI as sole source of carbon. Degradation was determined and confirmed by radiolabeled studies. Greater than 90% of the [*carboxymethyl*-2-^{14}C]-label of GI was released as $^{14}CO_2$ in 7 days using samples of sludge from the SBR. The cycle time required to biodegrade up to 7.5 mM GI in SBRs was reduced from 21 to <3 days. GI biodegradation was also established in an immobilized bacteria column inoculated with mixed liquor from a SBR; >99% GI removal was achieved at an influent concentration of 2.2 mM and a hydraulic retention time of <10 h. A pure bacterial culture was identified as *Xanthomonas maltophilia*. In liquid culture, *X. maltophilia* degraded up to 4.4 mM GI within 10 days and produced stoichiometric amounts of AMPA.
Method:	Sequencing batch reactor (SBR) inoculated with a mixture of sludges, soil, and sediments obtained from a glyphosate-manufacturing site acclimated to glyphosate waste waters since glyphosate biodegradation is maintained in waste treatment activated sludges used for treating waste waters at glyphosate manufacturing sites. US EPA (1983). "Methods for non-conventional pesticide analyses of industrial and municipal wastewater: method 127—determination of glyphosate in wastewater. US EPA, Publ. No. 440/1-83/079-C. pp. 1-10.
Data Quality:	Data obtained from experimental measurements.
References:	David B. Carson, Michael A. Heitkamp, and Laurence E. Hallas, "Biodegradation of N-phosphonomethyliminodiacetic acid by microorganisms from industrial activated sludge," Can. J. Microbiol., **43**, 97-101 (1997). Carson, D.B., Hallas, L.E., and Heitkamp, M.A., "Biodegradation of Glyphosate Intermediate, A Key Component of Glyphosate Process Waste," Monsanto Company Report No. MSL-11337 (1991). Carson, D.B., and Hallas, L.E., "Minimization of Glyphosate Process Waste I. Biotreatment of GI Centrate," Monsanto Company Report No. MSL-11338 (1991). Moench, William L. Jr., "Treatability of Glyphosate Waste Streams in a Municipal Bioreactor System," Monsanto Company Report No. MSL-15720 (1998). Rueppel, M.L., Brightwell, B.B., Schaefer, J., and Marvel, J.T., "Metabolism and degradation of glyphosate in soil and water," J. Agric. Food Chem., **25**, 517-522 (1977). Balthazor, T.M., and Hallas, L.E., "Glyphosate-degrading microorganisms from industrial activated sludge," Appl. Environ. Microbiol., **51**, 432-434 (1986). Cook, A.M., Daughton, C.G., and Alexander, M., "Phosphonate utilization by bacteria," J. Bacteriol., **133**, 85-90 (1978). Hallas, L.E., Hahn, E.M., and Korndorfer, C., "Characterization of microbial traits associated with glyphosate biodegradation in industrial activated sludge," J. Ind.

	Microbiol., **3**, 377-385 (1988). Heitkamp, M.A., Adams, W.J., and Hallas, L.E., "Glyphosate degradation by immobilized bacteria: laboratory studies showing feasibility for glyphosate removal from waste water," Can. J. Microbiol., **38**, 921-928 (1992). Strickland, Alan D. (Dow Chemical Company), "Determining biodegradability of iminodiacetic acid derivatives, degradable chelants, their uses and compositions," US Patent Application 1994-281054. Carson, David Bruce; Hallas, Laurence Edward; Heitkamp, Michael Alan (Monsanto Company), "Microbes and their use to degrade N-phosphonomethyliminodiacetic acid," US Patent Application 1992-890418. Velma E.A. Hayes, Nigel G. Ternan, and Geoffrey McMullan, "Organophosphonate metabolism by a moderately halophilic bacterial isolate," FEMS Microbiology Letters, **186**, 171-175 (2000). Agnieszka Obojska, Nigel G. Ternan, Barbara Lejczak, Pawel Kafarski, and Geoff McMullan, "Organophosphonate Utilization by the Thermophile *Geobacillus caldoxylosilyticus* T20," Applied and Environmental Microbiology, **68**, 2081-2084 (2002).
Remarks:	Several references have been provided that describe the biodegradation of glyphosate and similar organophosphonates by microorganisms. Glyphosate is transformed to aminomethylphosphonic acid (AMPA), a metabolite that is readily biodegradable in the environment. Although previous biotreatment studies had indicated GI to be more persistent, the first reference listed above describes the isolation and characterization of *Xanthomonas maltophilia* which also readily biodegrades GI from industrial activated sludges. Similar to glyphosate, GI is transformed to AMPA by the microorganisms. Other studies have shown the complete mineralization of AMPA by microorganisms in activated sludges from glyphosate-manufacturing sites under conditions of phosphate limitation. These studies demonstrate the biodegradation of GI. In shake flask assays, microbial isolates removed 1000 mg/L GI in <5 days.
Other:	

d. Transport between Environmental Compartments

Test Substances:	[^{14}C]GI (97.6% radiochemical purity) and [^{14}C]Glyphosate (98.0% radiochemical purity)
Result:	GI as well as glyphosate are both strongly adsorbed by most soil types with a high degree of binding affected slightly by soil pH and percentage organic matter. Combined with insignificant vapor pressure, neither GI nor glyphosate are likely to be found in air, and they have been shown to be not likely to leach through soils to reach groundwater or runoff to reach surface water.
Method:	Adsorption/Desorption; OECD Guideline for Testing of Chemicals, adopted 12 May 1981.
Data Quality:	Data obtained from experimental measurements.
References:	Livingston, C.L., Chott, K.A., and Schafer, T.R., "Australian Notification Base Testing Requirements for N-(Phosphonomethyl)iminodiacetic Acid (Glyphosate Intermediate). Part II: Adsorption/Desorption Data," Monsanto Company Report

	No. MSL-5393 (1986). Brightwell, B.B., and Malik, J.M., "Solubility, Volatility, Adsorption and Partition Coefficients, Leaching and Aquatic Metabolism of MON 0573 and MON 0101," Monsanto Company Report No. MSL-0207, R.D. #181 (1978). Rueppel, M.L., Brightwell, B.B., Schaefer, J., and Marvel, J.T., "Metabolism and degradation of glyphosate in soil and water," J. Agric. Food Chem., **25**, 517-522 (1977). Geisy, J.P., Dobson, S., and Solomon, K.R., "Ecotoxicological Risk Assessment for Roundup® Herbicide," Reviews of Environmental Contamination and Toxicology, **167**, 35-120 (2000). McConnell, J.S., and Hossner, L.R., "pH-Dependent Adsorption Isotherms of Glyphosate," J. Agric. Food Chem., **33**, 1075-1078 (1985). Nomura, N.S., and Hilton, H.W., "The Adsorption and Degradation of Glyphosate in Five Hawaiian Sugarcane Soils," Weed Research, **17**, 113-121 (1977).
Remarks:	Adsorption and desorption data were generated for GI, and for comparison purposes, the herbicides glyphosate and 2,4-D. The adsorption of GI on each of the three soils studies was substantial. The average percentage adsorbed from dilute aqueous solutions ranging in initial concentration from 0.04 ppm to 5 ppm ranged between 95.3 and 99.9 percent, and only 0.05 to 4.33 percent of the adsorbed chemical was desorbed in two sequential treatments with a solution of 0.01 M $CaCl_2$. This data was used to calculate values for the adsorption coefficient K'_{oc} which ranged from 9,050 to 309,023 for the different concentrations in all three soils. The values for the Freundlich constants K and 1/n were also determined by a computerized fit of the Freundlich equation to the adsorption data in the three soils. The Freundlich K constants were computed to be 68 (Spinks loamy sand), 99 (Dupo silt loam), and 575 (Drummer silty clay loam). These numbers indicated that GI does not have the potential for soil leaching. In comparison, although a difference was observed in the order of increasing adsorption among the soils studied, the overall adsorption of GI was found to be similar to that of glyphosate which had average adsorption percentages ranging between 87.8 and 99.0 percent, with corresponding K'_{oc} values ranging from 4,131 to 37,913. The Freundlich K constants for glyphosate were determined in the three soils to be 33 (Dupo silt loam), 324 (Drummer silty clay loam), and 660 (Spinks loamy sand). By contrast, the adsorption percentages for 2,4-D on the identical soils from a 5 ppm initial solution concentration were found to range between only 12 and 21 percent, with the corresponding K'_{oc} values calculated to range between 60 and 92.
Other:	

IV. Ecotoxicity

a. Acute Toxicity to Fish

Test Substance:	GI (97.6% sample purity)
Result:	96-hour LC_{50}: 75 mg/L (56-100 mg/L, 95% C.I.) 96-hour No-Effect Level: 32 mg/L, based on the lack of mortality and abnormal effects.
Method:	Static, acute toxicity Species: Rainbow Trout Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians. Stephan, C.E., Chairman. 1975. Committee on Methods for Toxicity Tests with Aquatic Organisms. US EPA, Ecological Research Series EPA-660/3-75-009, April, 1975.
Data Quality:	Reliable without restrictions. This is a well-documented US EPA guideline study conducted under GLP assurances. Study performed by ABC Laboratories, Columbia, MO (1985).
References:	"Acute Toxicity of Glyphosate Intermediate to Rainbow Trout (*Salmo gairdneri*)," Static Acute Toxicity Report No. 32877, Monsanto Study No. AB-85-029 (1985).
Remarks:	The no-effect level was based on the absence of mortality and abnormal clinical signs, i.e., surfacing, loss of equilibrium or dark discoloration in the treated fish. The water temperature, dissolved oxygen concentration, pH and ammonia concentration were within acceptable limits throughout the study. This material is considered to be slightly toxic to rainbow trout. The 24, 48, and 96-hour LC_{50} values for GI were all 75 mg/L. All results were based on the nominal test concentrations of 10, 18, 32, 56, and 100 mg/L. The no-effect concentration based on the lack of mortality and abnormal effects after 96 hours of exposure was 32 mg/L. The abnormal effects of mortality, surfacing, and/or quiescence were observed in the 56 and 100 mg/L test concentrations during the 96-hour exposure period. The rainbow trout were challenged with a reference compound, Antimycin A, to verify method precision. The 96-hour LC_{50} value for rainbow trout exposed to Antimycin A was 4.2×10^{-5} mg/L and was within the 95% confidence intervals reported in the literature. The fish were in good condition for testing. Ten fish, with a mean weight of 0.40 (±0.083) g and a mean standard length of 31 (±1.9) mm, were exposed to each test concentration and control. The dissolved oxygen concentrations ranged from 8.6 to 10.2 mg/L during the test. These values represented 80 and 92% saturation at 12 and 11 C, respectively, and were considered adequate for testing. The pH values ranged from 7.5 to 3.9. The pH values decreased with increasing test concentration.
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Test Substance:	GI (97.6% sample purity)
Result:	96-hour LC_{50}: 75 mg/L (56-100 mg/L, 95% C.I.)

	96-hour No-Effect Level: 32 mg/L, based on the lack of mortality and abnormal effects.
Method:	Static, acute toxicity Species: Bluegill Sunfish Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians. Stephan, C.E., Chairman. 1975. Committee on Methods for Toxicity Tests with Aquatic Organisms. US EPA, Ecological Research Series EPA-660/3-75-009, April, 1975.
Data Quality:	Reliable without restrictions. This is a well-documented US EPA guideline study conducted under GLP assurances. Study performed by ABC Laboratories, Columbia, MO (1985).
References:	"Acute Toxicity of Glyphosate Intermediate to Bluegill Sunfish (*Lepomis macrochirus*)," Static Acute Toxicity Report No. 32876, Monsanto Study No. AB-85-030 (1985).
Remarks:	The no-effect level was based on the absence of mortality and abnormal clinical signs, i.e., surfacing, loss of equilibrium or dark discoloration in the treated fish. The water quality parameters of temperature, dissolved oxygen and pH were measured throughout the test and were within acceptable limits. This material is considered to be slightly toxic to bluegill sunfish. The 24, 48, and 96-hour LC_{50} values for GI were all 75 mg/L. All results were based on the nominal concentrations of 10, 18, 32, 56, and 100 mg/L. The no-effect concentration based on the lack of mortality and abnormal effects after 96 hours of exposure was 32 mg/L. The abnormal effects of mortality, surfacing, and/or quiescence were observed in the 56 and 100 mg/L test concentrations during the 96-hour exposure period. The bluegill sunfish were challenged with a reference compound, Antimycin A, to verify method precision. The 96-hour LC_{50} value for bluegill sunfish exposed to Antimycin A was 10×10^{-5} mg/L and was within the 95% confidence intervals reported in the literature. The fish were in good condition for testing. Ten fish, with a mean weight of 0.14 (±0.044) g and a mean standard length of 19 (±1.8) mm, were exposed to each test concentration and control. The dissolved oxygen concentrations ranged from 6.8 to 9.5 mg/L during the test. These values represented 77and 108% saturation at 22 C, respectively, and were considered adequate for testing. The pH values ranged from 3.7 to 7.4, with pH levels in the test solutions decreasing as test concentrations increased.
Other:	Additional testing has been conducted on both glyphosate acid and GI to assure that the low levels anticipated in effluents would be non-toxic to marine species. Reference: "Toxicity of seven test materials to Sheepshead Minnows, *Cyprinodon variegates*," Toxicity Test Report Submitted to Monsanto Company, Report Number BP-78-4-029, EG&G Bionomics Marine Research Laboratory, April 1978. Ten sheepshead minnows, 7-10 mm standard length, were tested separately with either glyphosate or GI at concentrations of 0.6, 1.0, 3.2, 10, 32, 56, 100, 320, 560, and 1,000 ppm in static, unaerated seawater adjusted to pH 8.0. Salinity was 18% and temperature, 20 ± 1 C. Both glyphosate and GI had no effect on sheepshead

	minnows at concentrations ≤1,000 ppm. For GI and glyphosate, 96-hour EC_{50} values were reported as >1,000 ppm.

b. Acute Toxicity to Aquatic Invertebrates

Test Substance:	GI (97.6% sample purity)
Result:	24-hour EC_{50}: 750 mg/L (560-1000 mg/L, 95% C.I.) 48-hour EC_{50}: 700 mg/L (560-1000 mg/L, 95% C.I.) 48-hour No-Effect Level: 320 mg/L, based on the lack of mortality and abnormal effects.
Method:	Static, acute toxicity Species: *Daphnia magna* Methods of Acute Toxicity Tests with Fish, Macroinvertebrates and Amphibians. Stephan, C.E., Chairman. 1975. Committee on Methods for Toxicity Tests with Aquatic Organisms. US EPA, Ecological Research Series EPA-660/3-75-009, April, 1975.
Data Quality:	Reliable without restrictions. This is a well-documented US EPA guideline study conducted under GLP assurances. Study performed by ABC Laboratories, Columbia, MO (1985).
References:	"Acute Toxicity of Glyphosate Intermediate to *Daphnia magna*," Static Acute Toxicity Report No. 32878, Monsanto Study No. AB-85-031 (1985). F.D. Hileman, D.R. Grothe, C.A. Ritchie, and M.W. Tucker, "Analysis of the Components Contributing to the Aquatic Toxicity in the Fayetteville Effluent," Monsanto Report No. MSL-7786 (1988).
Remarks:	The no-effect level was based on the absence of mortality and abnormal clinical signs, i.e., surfacing, clumping of the *Daphnia* together and daphnids laying on the bottom of the test chambers. The water temperature (20 C), dissolved oxygen concentration, pH and ammonia concentration were within acceptable limits throughout the study. This material is considered to be practically non-toxic to *Daphnia magna*. Results were based on the nominal concentrations of 100, 180, 320, 560, and 1000 mg/L. The dissolved oxygen concentrations ranged between 8.2 and 9.2 mg/L. These values represented 87 and 100 percent saturation at 20 C, respectively, and were considered adequate for testing. The pH values decreased with increasing GI levels and ranged from 3.6 to 8.6.
Other:	Additional testing has been performed on both glyphosate acid and GI to assure that the low levels anticipated in effluents would be non-toxic to marine species. Reference: "Toxicity of seven test materials to Mysid Shrimp, *Mysidopsis bahia*," Toxicity Test Report Submitted to Monsanto Company, Report Number BP-78-4-032, EG&G Bionomics Marine Research Laboratory, April 1978. Reference: "Toxicity of seven test materials to the white sea urchin, *Tripneustes esculentus*," Toxicity Test Report Submitted to Monsanto Company, Report Number BP-78-4-030, EG&G Bionomics Marine Research Laboratory, April 1978.

	For GI and glyphosate, 96-hour EC_{50} values of >1,000 ppm were determined for the white sea urchin (*Tripneustes esculentus*) and mysid shrimp (*Mysidopsis bahia*).

c. Toxicity to Aquatic Plants

Test Substance:	GI (pure compound, analytical grade quality)
Result:	96-hour EC_{50}: 100 – 320 mg/L based on chlorophyll content 96-hour EC_{50}: 140 mg/L (51-379 mg/L, 95% C.I.) based on cell count, practically non-toxic
Method:	Static, acute toxicity Species: Marine Alga, *Skeletonema costatum* US EPA. 1976. Bioassay procedures for the ocean disposal permit program. EPA-600/9-76-010. 96 p.
Data Quality:	Reliable with restrictions. This is a well-documented study following test procedures of US EPA guidelines (1976) conducted without GLP assurances.
References:	"Toxicity of seven test materials to the marine alga, *Skeletonema costatum*," Toxicity Test Report Submitted to Monsanto Company, Report Number BP-78-4-031, EG&G Bionomics Marine Research Laboratory, April 1978.
Remarks:	Beginning cell numbers in test flasks were 2 x 10^4 cells/mL. Cultures were incubated at 20 ± 1 C under 2,000 lux illumination. Salinity of the medium was 30%. Duplicate cultures were employed for each of the test concentrations at 3.2, 10, 32, 100, 320, and 560 mg/L, and control. The percentage change of in vivo chlorophyll α in exposed cultures as compared to the control at 24, 48, 72, and 96 hours, and the increase or decrease of cell numbers in exposed cultures as compared to the control at 96 hours was measured. A separate test was conducted in which cultures of the alga were exposed to the reference toxicant dodecyl sodium sulfate (DSS) under the same test conditions, and the range of calculated 96-hour EC_{50}'s for DSS (1.6-2.5 ppm, based on decrease cell numbers) showed the algal culture was in satisfactory condition for testing. Glyphosate, tested separately under the same conditions, resulted in 96-hour EC_{50} values for marine alga of 1.2 mg/L based on chlorophyll content, and 1.3 mg/L based on cell count. Based on studies conducted with glyphosate on several algal species, *Skeletonema* has been found to be more sensitive to glyphosate than freshwater algal species (Giesy et al, 2000).
Other:	

V. Toxicological Data

a. Acute Toxicity

Test Substance:	GI (97.28% purity, lot no. LBIG-12-026)
Result:	Inhalation exposure of rats to an atmospheric concentration of 6.1 mg/L GI for 4 hours did not cause any mortality. Thus, the inhalation LC_{50} is considered to be greater than 6.1 mg/L. GI is not considered to present a significant acute inhalation hazard.
Method:	A group of 5 male and 5 female Sprague Dawley (CD®) albino rats were exposed to a dust aerosol atmosphere of GI for 4 hours. The average gravimetrically determined chamber concentration was approximately 6.1 mg GI/L of air. A second group of 5 male and 5 female rats were exposed to air only and served as the control. The animals were observed for mortality and clinical signs of toxicity during the exposure and twice daily during the 14-day postexposure period. Individual body weights were recorded prior to exposure and on postexposure days 2, 3, 4, 7 and 14. On postexposure day 14, all animals were sacrificed and given a complete gross necropsy examination.
Data Quality:	Reliable without restrictions. This is a well-documented guideline study conducted under GLP assurances. Study performed by International Research and Development Corporation, Mattawan, MI (1984).
References:	"Glyphosate Intermediate: Acute Inhalation Toxicity Study in Rats," Monsanto Company Report No. IR-82-192 (IRDC #401-188).
Remarks:	No mortality resulted from the inhalation exposure to 6.1 mg/L of GI. Thus no further exposures were considered to be necessary. Approximately 50% of the particles were less than 10 microns in diameter with a mass median aerodynamic diameter of 7.2 microns. Body weights of test-material exposed animals were depressed below their pre-exposure weights on postexposure days 2-4. By day three or four, however, all animals were gaining weight at a rate equivalent to controls. The primary clinical signs of toxicity in treated animals were nasal discharge and colored material about the eyes, nose and mouth. No signs were observed in control animals. The only gross necropsy observations of note were red foci on the lung and thymus. Although these lesions were observed at a greater frequency in the treated group, they were also observed in controls.
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Test Substance:	GI (98.05% purity, lot no. 4-86-587)
Result:	Oral, rat LD_{50}: 2,200 mg/kg (slightly toxic, US EPA pesticide category III) Dermal, rabbit LD_{50}: >5,000 mg/kg (practically nontoxic, US EPA pesticide category IV) Eye irritation, rabbit 24-hour: severely irritating, US EPA pesticide category I Skin irritation, rabbit 24-hour exposure: nonirritating, US EPA pesticide category IV

Method:	Methods are described in the following section for remarks.
Data Quality:	Reliable without restrictions. This is a well-documented US EPA guideline study conducted under GLP assurances. Study performed by Bio/dynamics, Inc., East Millstone, NJ (1986).
References:	"Glyphosate Intermediate: Acute Toxicity & Irritation Studies," Monsanto Company Report No. BD-86-172 (B/d No. 6563-86 through 6566-86).
Remarks:	When GI diluted with aqueous 1% methyl cellulose solution was administered by gavage to fasted albino rats of both sexes, the acute LD_{50} was calculated to be 2200 milligrams per kilogram (mg/kg). The dermal LD_{50} was estimated to be greater than 5000 mg/kg when albino rabbits received a continuous 24-hour application of GI moistened with 0.9% saline on intact skin. Thus, GI is considered to be slightly toxic by ingestion in single doses and practically non-toxic by single dermal applications. When 71.6 mg (the 0.1 mL volume equivalent) of GI was placed into the conjunctival sac of the rabbit eye, severe irritation resulted. Two of the six rabbits' eyes cleared by post exposure day 21. Three of the animals continued to exhibit slight corneal opacity at termination of the study (day 21) while the sixth animal continued to show necrosis at day 21. When 0.5 gram of GI moistened with 0.5 mL of a 0.9% saline was held in continuous 4-hour contact with rabbit skin, no irritation was observed. Because it is severely irritating to eyes, care, including the use of protective equipment, should be taken to prevent eye contact with GI. In case of contact, flush immediately with large volumes of water for at least 15 minutes and call a physician.
Other:	

b. Repeated Dose Toxicity

Test Substance:	GI (97.97% purity)
Result:	NOEL (systemic): 150 mg/kg/day No sign of systemic toxicity at any dermal dose level.
Method:	Species: Albino rat Strain: Sprague/Dawley Number used in study: 80 (40 male, 40 female) Test group size: 10/sex GI, suspended in mineral oil, was applied to the shaved backs of male and female rats for 6 hours/day, 5 days/week for 4 weeks at dose levels of 0, 25, 150 mg/kg/day and for 16 days at 500 mg/kg/day. Application sites were not covered, but animals were fitted with collars to prevent ingestion of the test material. Animals were observed once per week for signs of toxicity and twice daily for mortality. Body weights and food consumption were recorded weekly. At the termination of the study, all vehicle control, low, and mid dosage group animals were sacrificed and blood was collected. A complete gross necropsy examination was performed on all animals. Weights of the liver, kidneys, heart, brain, and testes with epididymides were recorded. All of the retained tissues from all animals in the control and mid dose level groups were examined microscopically.
Data Quality:	Reliable without restrictions. This is a well-documented US EPA guideline study

	conducted under GLP assurances. Study performed by Environmental Health Laboratory, St. Louis, MO (1987).
References:	M.S. Reyna, and C.W. Johnson, "Rangefinder and One Month Dermal Studies of Glyphosate Intermediate in Albino Rats," Monsanto Company Report No. MSL-6983 (1987).
Remarks:	Dermal lesions were seen at all dose levels in males and at 150 and 500 mg/kg/day in females. The 500 mg/kg/day group was terminated on day 16 because of the severity of the dermal lesions. Body weight and food consumption were decreased in the 500 mg/kg/day group. Significant increases in white blood cell and absolute lymphocyte count were detected in the 150 mg/kg/day group, however, these findings were considered to be a secondary response to the dermal irritation. No signs of systemic toxicity were observed at any dose level. Under the conditions of this study, the 150 mg/kg/day treatment level was considered to be the systemic no-observable-effect level (NOEL).
Other:	Dermal Sensitization Study in Guinea Pigs Method: A study designed to evaluate the potential of GI to produce skin sensitization following repetitive dermal exposure was completed. During both the induction and challenge phases, 0.2 cc of GI (pure compound, lot LUIG 01-003) was moistened with 0.2 mL saline and applied to the shaved backs of 5 male and 5 female Hartley guinea pigs. The induction phase consisted of exposures for 6 hours/day, 3 days/week, for 3 weeks. Following a 2 week rest period, the same animals were challenged with GI for 6 hours on previously untreated sites. The animals were observed twice daily for mortality and weekly for signs of toxicity. Dermal irritation was scored (on a scale of 0 to 3) at 24 and 48 hours after each application of test material. GLP/QA review: Yes. Results: No dermal responses were seen in the negative control (distilled water) or GI treated animals during the induction or challenge phases. The results indicated that GI does not produce dermal sensitization in guinea pigs. Reference: "Glyphosate Intermediate: Dermal Sensitization Study in Guinea Pigs," Monsanto Company Report No. BD-85-14 (1985).

c. Genetic Toxicity

Test Substance:	GI (pure compound, lot no. 178)
Result:	Under the conditions of this assay, GI is not considered to be genotoxic in the rat hepatocyte primary culture/DNA repair assay.
Method:	Primary liver cell cultures were derived from the livers of 2 adult male Fisher-344 rats. Following in situ perfusion of the livers with collagenase to digest connective tissue, the isolated liver cells were seeded into culture dishes. After 1.5 to 2 hours, non-viable cells were washed out of the culture and the viable cells employed immediately for the DNA repair assay. The positive control material was diluted with acetone. GI was diluted directly with culture media. For the DNA repair assay, triplicate cultures of liver cells were simultaneously exposed to tritiated thymidine and ten concentrations of GI ranging from 0.1 to 5000 µg/mL in the preliminary assay and six concentrations ranging from 10 to 2500

	μg/mL in the replicate assay for 20 hours at 37 C. A positive control (2-AAF) and a media control were also tested. After exposure, all cultures were washed with media, swelled in hypotonic solution, fixed, mounted on slides, dipped into Kodak NTB-2 emulsion and exposed at –20 C for 7 days prior to development. Cells were stained in methyl-green Pyronin Y. Quantitative autoradiographic grain counting was performed using a colony counter coupled to a microscope and computer. Fifty morphologically unaltered cells on a randomly selected area of each slide were counted. Net nuclear grain counts were calculated by subtracting the highest of two cytoplasmic counts from the nuclear count. A total of 150 cells/concentration were scored in each assay. A test compound is considered positive if a net grain count of at least five is consistently observed at non-toxic doses. The percent of cells in repair was calculated as the percentage of cells with at least five net grains per nucleus.
Data Quality:	Reliable without restrictions. This is a well-documented study conducted under GLP assurances. Study performed by SRI International, Menlo Park, CA (1985).
References:	"Glyphosate Intermediate: Hepatocyte Primary Culture DNA Repair Assay," Monsanto Company Report No. SR-85-157 (SRI #LSC-8747-2).
Remarks:	Cytotoxicity was observed at 5000 μg/mL in the preliminary assay. No cytotoxicity was observed in the replicate assay. GI turned the culture media acidic at concentrations of 500 μg/mL and above in both assays. Net grain counts were negative at all concentrations of GI scored and for the media control. In contrast, the positive control material (2-AAF) elicited a strong positive response in both assays (25.5 and 28.4 net grains), indicating that the assay is sensitive to a known genotoxic compound. DNA repair was not measured at concentrations of 0.1 to 1.0 μg/mL GI in the preliminary assay since DNA repair was not seen at higher concentrations. Visual examination of slides in these groups confirmed the absence of DNA repair.
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Test Substance:	GI (98.4% purity)
Result:	Microbial mutagenic assay (Ames): GI is considered nonmutagenic in this test system. No mutagenic activity was observed in any of the tester strains with or without metabolic activation.
Method:	Approximately 10^8 cells from an overnight culture of each indicator strain were added to separate test tubes containing 2.0 mL of molten agar supplemented with biotin and a trace of histidine. For non-activation tests, at least four dose levels of the test compound were added to the contents of the appropriate tubes and poured over the surfaces of selective agar plates. In activation tests, a minimum of four different concentrations of the test chemical were added to the appropriate tubes with cells. Just prior to pouring, an aliquot of reaction mixture (0.5 mL containing the 9,000 x g liver homogenate) was added to each of the activation overlay tubes, which were then mixed, and the contents poured over the surface of a minimal agar plate and allowed to solidify. The plates were incubated for 48 hours at 37 C, and scored for the number of colonies growing on each plate. The concentrations of GI tested ranged from 0.1 to 500 μg per plate. Positive and solvent controls using both directly active positive chemicals and those that require metabolic activation were run with each assay.

Data Quality:	Reliable with restrictions. This is a well-documented study following standard testing procedures (1977) conducted without GLP assurances.
References:	"Mutagenicity Evaluation of CP 41820," Monsanto Company Report No. BIO-77-212, LBI Project No. 2683 (Litton Bionetics, Inc., Kensington, MD), August, 1977. Ames *et al.*, Mutation Research, **31**, 347 (1975).
Remarks:	The objective of this study was to evaluate the test compound for genetic activity in microbial assays with and without the addition of mammalian metabolic activation preparations. GI was evaluated at 5 dose levels in each of 5 Salmonella bacterial strains (TA-1535, TA-1537, TA-1538, TA-98, and TA-100) and one strain of Saccharomyces yeast (D4). Assays were conducted with and without incorporation of a microsomal enzyme activation system. Appropriate positive and negative controls were employed in the study.
Other:	

d. Reproductive Toxicity

Test Substance:	GI (pure compound, lot no. LUIG 03014)
Result:	Based upon the results of this study, the NOEL for "irritant" responses and for reproductive impairment are 0.86 mg/m^3 and 9.6 mg/m^3 of air, respectively.
Method:	13-Week Inhalation Toxicity/Reproduction Study in Rats Animal Species: Albino rats This study consisted of two parts, a 13-week toxicity study and a one-generation reproduction study. In the toxicity study, GI was administered as a dust aerosol to groups of 25 male and 20 female albino rats at target exposure concentrations of 1.0, 10, or 100 mg/m^3 of air. The control group was exposed to room air only. Exposures were conducted six hours/day, five days/week for 13 consecutive weeks. Test animals were observed twice daily for mortality and signs of toxicity. A detailed physical examination of each animal was performed once each week. All animals dying spontaneously and all animals sacrificed at the week 6 interim and week 13 terminal sacrifices received a complete gross post-mortem examination. The reproductive phase of the study consisted of additional groups of animals exposed in the same chambers along with the animals from the 13-week toxicity study. At each exposure level there were 15 exposed males (from the 13-week toxicity phase), 25-non-exposed males, 25 exposed females, and 30 non-exposed females. Matings were conducted after approximately 10 weeks of exposure between treated males and untreated females, treated females and untreated males, and untreated males and untreated females. Treated males were exposed for 6 hours/day, 5 days/week, with matings occurring during the night between exposures. This exposure regimen was continued until the scheduled 13-week sacrifice. Treated females were exposed 6 hours/day, 5 days/week, until evidence of copulation was observed, after which they were exposed seven days/week until sacrificed at the termination of weaning, except for gestation day 20 through lactation day 3, when they were not exposed. All animals were observed twice daily for mortality and clinical signs of toxicity. Following the 13-week exposure period, 5 male rats from each of the treated and control groups were selected for an evaluation of reproductive function. Testicular and epididymal weights were recorded, followed by collection of semen samples. Sperm number, motility, and morphology were evaluated.
Data Quality:	Reliable without restrictions. This is a well-documented guideline study conducted

	under GLP assurances. Study performed by International Research and Development Corporation, Mattawan, MI (February, 1986).
References:	"Glyphosate Intermediate: 13-Week Inhalation Toxicity/Reproduction Study in Rats," Monsanto Company Report No. IR-83-084 (IRDC #401-212).
Remarks:	The study consisted of a 13-week toxicity study and a 1-generation reproduction study – animals were exposed concurrently. Overall mean analytical exposure concentrations were 0.86, 9.6, and 102 mg/m^3 of air. The following results were noted in high exposure level animals – increased mortality, decreased body weight, decreased number of viable pups/dam, pup weight, and pup survivability, and altered male mating behavior. These effects may have resulted from the maternal toxicity observed at the high dose level. All litter parameter values for the low and mid exposure level groups were comparable to control group values from birth through lactation. Observation of pups throughout lactation failed to disclose any abnormalities considered exposure-related. Effects observed at both the mid and high exposure levels included pulmonary inflammatory cell infiltrate, tracheitis, bronchitis, nasal mucosal metaplasiz, and olfactory mucosal atrophy. These effects were considered to be irritant responses due to direct contact of the test material with the respiratory passages. As such, they were not considered to represent systemic toxic effects resulting from absorption of the test material.
Other:	

e. Developmental Toxicity

Test Substance:	GI (96.86% purity, lot no. LC-1G-01-002)
Result:	Significant maternal toxicity was observed in the high-dose (400 mg/kg/day) group and signs of fetotoxicity were observed in the high- and mid-dose groups. Although the total number of fetuses with malformations increased in a dose-related manner, none of the malformations were observed at abnormal litter or fetal frequencies. The teratogenic no-observable effect level (NOEL) was considered to be 400 mg/kg/day.
Method:	GI was administered in 0.5% carboxymethyl cellulose by stomach tube to three groups of 25 mated Charles River COBS® CD® female, albino rats on days six through 15 of gestation. Dosage levels were 0 (vehicle control), 25, 100, and 400 mg/kg body weight/day at a constant dosing volume of 10 mL/kg. On gestation day 20, all surviving dams were killed and the uterus and ovaries were exposed by abdominal incision. The number and location of viable and nonviable fetuses, early and late resorptions, total implantations and corpora lutea were recorded. The fetuses were then removed and the abdominal and thoracic cavities examined grossly. Those animals that died on study were given a similar examination. All fetuses were individually weighed, sexed and examined for external malformations and variations. Approximately one-half of the fetuses were given soft tissue examinations and the other half were macerated with potassium hydroxide for skeletal examinations. Fetal findings were classified as malformations or developmental variations.
Data Quality:	Reliable without restrictions. This is a well-documented guideline study conducted under GLP assurances. Study performed by International Research and

	Development Corporation, Mattawan, MI (1984).
References:	"Glyphosate Intermediate: Teratology Study in Rats," Monsanto Company Report No. IR-83-109 (IRDC #401-213).
Remarks:	Examination of the reproductive parameters, i.e. viable fetuses, postimplantation loss, total implantations and the number of corpora lutea per dam revealed no treatment-related effects. The mean fetal body weight in the high-dose group was slightly reduced (~9%) when compared with control. This fetotoxic response was considered to be related to the maternal toxicity observed in the high-dose group. The fetal sex distribution was within the normal range. The total number of malformations and the total number of fetuses with malformations increased in a dose-related manner; however, the number of litters with malformations was not increased. There were no more than three litters per group with malformations of any type, nor more than one litter per group with a specific malformation and often one fetus in the litter had two or more of the malformations. All of the malformations are commonly observed in the fetal rat and the incidences of all but one aberration fell within the range of historical control values. The number of fetuses in the high-dose group with "bent rib" was slightly above the historical control incidence (3.6 vs. 3.5%), however, all the fetuses came from the same litter. None of the aberrations were considered to be related to test material administration. A similar pattern of increased total numbers of genetic and developmental variations was observed in the mid- and high-dose groups. The number of fetuses in the mid- and high-dose groups with one of the variations, i.e. hyoid unossified, while not statistically different from controls, were increased over the historical control incidence. This was considered to be a result of maternal toxicity rather than a teratogenic response.
Other:	

APPENDIX

Reference 1

Gary M. Williams, Robert Kroes, and Ian C. Munro. "Safety Evaluation and Risk Assessment of the Herbicide Roundup® and Its Active Ingredient, Glyphosate, for Humans," Regulatory Toxicology and Pharmacology, **31,** 117-165 (2000). Abstract available online at http://dx.doi.org/10.1006/rtph.1999.1371

Reference 2

"Summary of Human Risk Assessment and Safety Evaluation on Glyphosate (and Roundup® Herbicide)", Monsanto Company Backgrounder, November, 2001.

Reference 3

"Summary of Ecotoxicological Risk Assessment for Roundup® Herbicide," Monsanto Company Backgrounder, November, 2001.

Reference 4

"Glyphosate and Standard Toxicology Studies," Monsanto Company Backgrounder, September, 2002.

Reference 5

"Glyphosate and Environmental Fate Studies," Monsanto Company Backgrounder, April, 2003.

Reference 1

Gary M. Williams, Robert Kroes, and Ian C. Munro. "Safety Evaluation and Risk Assessment of the Herbicide Roundup® and Its Active Ingredient, Glyphosate, for Humans," Regulatory Toxicology and Pharmacology, **31,** 117-165 (2000). Abstract available online at http://dx.doi.org/10.1006/rtph.1999.1371

Gary M. Williams, Robert Kroes, and Ian C. Munro. "Safety Evaluation and Risk Assessment of the Herbicide Roundup® and Its Active Ingredient, Glyphosate, for Humans," Regulatory Toxicology and Pharmacology, **31,** 117-165 (2000). Abstract available online at http://dx.doi.org/10.1006/rtph.1999.1371

Abstract:

Reviews on the safety of glyphosate and Roundup herbicide that have been conducted by several regulatory agencies and scientific institutions worldwide have concluded that there is no indication of any human health concern. Nevertheless, questions regarding their safety are periodically raised. This review was undertaken to produce a current and comprehensive safety evaluation and risk assessment for humans. It includes assessments of glyphosate, its major breakdown product [aminomethylphosphonic acid (AMPA)], its Roundup formulations, and the predominant surfactant [polyethoxylated tallow amine (POEA)] used in Roundup formulations worldwide. The studies evaluated in this review included those performed for regulatory purposes as well as published research reports. The oral absorption of glyphosate and AMPA is low, and both materials are eliminated essentially unmetabolized. Dermal penetration studies with Roundup showed very low absorption. Experimental evidence has shown that neither glyphosate nor AMPA bioaccumulates in any animal tissue. No significant toxicity occurred in acute, subchronic, and chronic studies. Direct ocular exposure to the concentrated Roundup formulation can result in transient irritation, while normal spray dilutions cause, at most, only minimal effects. The genotoxicity data for glyphosate and Roundup were assessed using a weight-of-evidence approach and standard evaluation criteria. There was no convincing evidence for direct DNA damage in vitro or in vivo, and it was concluded that Roundup and its components do not pose a risk for the production of heritable/somatic mutations in humans. Multiple lifetime feeding studies have failed to demonstrate any tumorigenic potential for glyphosate. Accordingly, it was concluded that glyphosate is noncarcinogenic. Glyphosate, AMPA, and POEA were not teratogenic or developmentally toxic. There were no effects on fertility or reproductive parameters in two multigeneration reproduction studies with glyphosate. Likewise there were no adverse effects in reproductive tissues from animals treated with glyphosate, AMPA, or POEA in chronic and/or subchronic studies. Results from standard studies with these materials also failed to show any effects indicative of endocrine modulation. Therefore, it is concluded that the use of Roundup herbicide does not result in adverse effects on development, reproduction, or endocrine systems in humans and other mammals. For purposes of risk assessment, no-observed-adverse-effect levels (NOAELs) were identified for all subchronic, chronic, developmental, and reproduction studies with glyphosate, AMPA, and POEA. Margins-of-exposure for chronic risk were calculated for each compound by dividing the lowest applicable NOAEL by worst-case estimates of chronic exposure. Acute risks were assessed by comparison of oral LD50 values to estimated maximum acute human exposure. It was concluded that, under present and expected conditions of use, Roundup herbicide does not pose a health risk to humans.

Reference 2

"Summary of Human Risk Assessment and Safety Evaluation on Glyphosate (and Roundup® Herbicide)", Monsanto Company Backgrounder, November, 2001.

Backgrounder

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Summary of Human Risk Assessment and Safety Evaluation on Glyphosate (and Roundup® Herbicide)

Three internationally recognized toxicologists have completed and published a peer-reviewed safety evaluation and risk assessment of glyphosate and the most commonly sold Roundup herbicide formulations. The authors (see biographical data below*) reviewed Monsanto studies which had previously been reviewed by regulatory authorities around the world (see below).** In addition, they reviewed regulatory and scientific organization reports as well as a wide array of studies conducted by independent researchers using information obtained from public literature. Over a two-year period, they examined and critiqued 188 documents to prepare a comprehensive evaluation of glyphosate.

The basic Roundup formulation that has been used around the world for 30 years contains the active ingredient glyphosate (in the form of its isopropylamine salt), water and a surfactant (POEA or polyethoxylated alkyl amine). For most agricultural and industrial uses, Roundup formulations contain 41 percent glyphosate isopropylamine salt and must be diluted with water before application. The ready-to-use product sold to homeowners contains a 1 percent solution of glyphosate isopropylamine salt. The reviewers conducted a risk assessment of the formulated product, the surfactant, the active ingredient and its major breakdown component, AMPA (aminomethyl phosphonic acid). They considered exposures during both application of the product and consumption of treated food crops.

The paper, "Safety Evaluation and Risk Assessment of the Herbicide Roundup and Its Active Ingredient, Glyphosate, for Humans," by Gary M. Williams, Robert Kroes, and Ian C. Munro, was published in *Regulatory Toxicology and Pharmacology*, (2000) Volume 31, pages 117-165.

Key findings of this study include:

- **Glyphosate is not a carcinogen.** – "*The chronic toxicity and oncogenic potential of glyphosate ... have been evaluated by a number of regulatory agencies and by international scientific organizations. Each of these groups has concluded that glyphosate is not carcinogenic.*" *(p. 126)* This is based on long-term studies in which mice and rats were fed extremely high doses of glyphosate every day for two years. The U.S. EPA has placed glyphosate in Category E ("evidence of non-carcinogenicity for humans"), the most favorable carcinogenicity category possible.

- **Roundup has very low acute toxicity, which means very high exposure is required to cause an adverse effect.** The reviewers evaluated the potential short-term (acute) exposure and risk to herbicide applicators and children living on a farm. These two population groups have the maximal opportunity for exposure because they are most likely to come in contact with herbicide sprays and residues. In addition, children age 1 to 6 are assumed to have the highest dietary exposure because they eat more of some foods per body weight than other age groups. In the exposure assessment, it was assumed that the child occasionally enters a recently sprayed farm field and stays there for up to five hours, playing or helping a parent. The authors compared the acute oral LD50s of glyphosate and POEA to a calculated acute exposure to these two subgroups. (LD50 is a standard for expressing the toxicity of a compound.) The calculated acute exposure of the two subgroups in the on-farm study that have maximal assumed opportunity for exposure were estimated to be 40,000 to 50,000 times lower than the LD50 of glyphosate and 7,360 to 13,200 times lower than the LD50 of POEA. *(p. 159-160)* Other studies showed that serious effects occurred only when large amounts of concentrated Roundup (e.g. ≥ 41%) were intentionally ingested. *(p. 149)*

- **Roundup poses minimal risk of injury.** *"Roundup is placed in U.S. EPA's least toxic category (IV) for acute oral, dermal and inhalation toxicity. Thus, the Roundup formulation is considered to be practically nontoxic by all these routes of exposure. ... POEA is considered to be only slightly toxic and does not represent an acute toxicity hazard." (p. 129) "Results from several investigations establish that the acute toxicity and irritation potential of Roundup herbicide in humans is low." (p. 148)* With Roundup formulations containing the POEA surfactant, there is potential for eye irritation if the spray is misdirected or if splashing occurs during mixing with water. The surfactant POEA, in its concentrated form, is severely irritating to eyes, but the researchers reported that *"POEA is not used in concentrated form but rather is formulated at lower concentrations into an end-use product (Roundup) and later diluted to very low levels, rendering it significantly less irritating ... When diluted to a concentration commonly used for most spraying applications (~1%), Roundup was shown to be only minimally irritating to eyes and essentially non-irritating to skin." (p. 129)* The researchers also addressed a statistic commonly cited by pesticide activist groups, which identify Roundup as a leading cause of pesticide illness in California. *"Careful examination of the California data further indicates that the number of cases reported simply reflects greater use of the product relative to other herbicides and shows that glyphosate has relatively low toxicity among pesticides used in the State ... In 1994, for example, glyphosate exposure was reported in only 25 cases, of which only 13 were considered "definite or probable." Eleven of the 13 cases involved only minor and reversible eye irritation; the other two cases were a headache and an apparent misdiagnosis of reaction to hydrocarbon solvent, which is not an ingredient in Roundup."* The researchers noted that the California Department of Pesticide Regulation, which compiles pesticide illness figures, noted in its 1994 report that the majority of people reporting Roundup exposure experienced only irritant effects and that in 13 years of record keeping, there had been no hospitalization linked to Roundup. *(pp. 147-148)*

- **Glyphosate does not bioaccumulate.** *"The potential for systemic exposure is limited by the combination of poor absorption and rapid excretion of glyphosate after oral and/or dermal contact." (p. 124)* As glyphosate is not stored in the body, any exposure from skin contact or inhalation would be quickly eliminated by humans and animals.

- **Glyphosate does not adversely affect reproduction or development.** *"Results from several studies have established that glyphosate is not a reproductive or developmental toxicant." (p. 128)* In developmental toxicity studies, and in multi-generation animal studies in which high doses were fed to laboratory animals, *"there were no effects on fertility or reproductive parameters, and glyphosate did not produce birth defects." (pp. 127-128)* The developmental toxicity of the surfactant predominantly used in Roundup formulations worldwide (POEA) and its possible effects on the reproductive system have also been evaluated in animal studies. *"There is no evidence that the surfactant or Roundup herbicide adversely impacts reproductive function." (p. 131)* The authors devoted several paragraphs to their critique of a rabbit study often cited by pesticide critics to imply sperm count reduction. (Yousef et al., 1995) *"There were a number of serious deficiencies in the design, conduct and reporting of this study which make the results uninterpretable. ... the data from this study cannot be used to support any meaningful conclusions." (p. 127-128)*

- **Children are not at greater risk.** *"The U.S. EPA has recently evaluated tolerance petitions under the Food Quality Protection Act of 1996 (FQPA) (Public Law 104-170) which includes special provisions to protect infants and children. The U.S. EPA concluded that there is "reasonable certainty" that no harm will occur from aggregate exposure to glyphosate (U.S. EPA 1997a, 1998a)." (p. 128)* EPA also concluded that the currently applied safety factor of 100 is adequate to protect children. *"There was no suggestion of increased severity of effect in infants or children or of increased potency or unusual toxic properties of glyphosate in infants and children." (p.156)*

- **There is no evidence of endocrine disruption.** *"The endocrine-modulating potential of glyphosate has been evaluated in a variety of studies including* in vitro *assays and standard* in vivo *toxicology studies. The* in vivo *studies comprehensively assess endocrine functions that are required for reproduction, development, and chronic health. Glyphosate produced no effects in* in vitro *assays, and there was no indication of changes in endocrine function in any of the* in vivo *studies. Results from standard studies with AMPA, Roundup herbicide, and the POEA surfactant also failed to show any effects indicative of endocrine modulation. Therefore, it is concluded that the use of Roundup herbicide has no potential to produce adverse effects on endocrine systems in humans nor in other mammals." (p.143)*

- **There is no synergistic adverse effect.** Herbicides sometimes are applied in combination with other herbicides, raising the question of whether the combination creates a synergistic effect (more than an additive response). *"The toxicity of glyphosate has been evaluated in combination with several surfactants and/or other herbicides ... it is concluded that the simultaneous exposure of glyphosate and other materials does not produce a synergistic response." (p. 145)*

REFERENCES IN ITALICS THROUGHOUT THIS DOCUMENT REFER TO STATEMENTS OR CONCEPTS EXPRESSED BY THE AUTHORS OF "SAFETY EVALUATION AND RISK ASSESSMENT OF THE HERBICIDE ROUNDUP AND ITS ACTIVE INGREDIENT, GLYPHOSATE, FOR HUMANS."

***BIOGRAPHICAL DATA:**

Gary M. Williams, M.D., is Director of Environmental Pathology and Toxicology and Head of the Program on Medicine, Food and Chemical Safety at New York Medical College, Valhalla., N.Y. He is a board-certified pathologist, physician and toxicologist in the United States and has also been certified as an Expert in Toxicology by the French Ministere des Affaires. He has served as an editor or editorial board member for more than 25 scientific journals and papers. Williams has also organized more than 20 scientific meetings and conferences around the world, many of which discussed safety assessments of pharmaceuticals and chemicals, and cancer screening tests and prevention.

Robert Kroes, Ph.D., is the Director of the Research Institute for Toxicology at Universiteit Utrecht in The Netherlands. He is board-certified in toxicology and pathology and specializes in toxicology, oncology and risk assessments. He served for seven years as Deputy Director General of the Dutch National Institute of Public Health and Environmental Protection. He has served as a member of more than 20 international expert panels on toxicology, oncology and environment and health, including groups impaneled by the World Health Organization, the Food and Agriculture Organization of the United Nations, the Organization for Economic Cooperation and Development, and the European Union. He is an editorial board member of 13 scientific periodicals.

Ian C. Munro, Ph.D., is President of CANTOX Health Sciences International and a professor in the Department of Nutritional Sciences at the University of Toronto, Ontario, Canada. He is a Fellow at The Academy of Toxicological Sciences and the Royal College of Pathologists in London. He has more than 150 scientific publications in the fields of toxicology and risk assessment. He formerly held senior positions at Health and Welfare Canada as Director of the Bureau of Chemical Safety and Director General of the Food Directorate, Health Protection Branch. He also was Director of the Canadian Centre for Toxicology at Guelph, Ontario. Munro has served on more than 30 expert panels, nationally and internationally, including those of the World Health Organization, the International Agency for Research on Cancer and the U.S. National Academy of Sciences, where he chairs a subcommittee. He is a recipient of the "International Achievement Award" of the International Society of Regulatory Toxicology and Pharmacology. He has served on the editorial boards of Neurotoxicology, the Journal of the American College of Toxicology, and the Journal of Environmental Pathology and Toxicology.

** *"Government regulatory agencies in several countries, international organizations, and other scientific institutions and experts have reviewed the available scientific data and independently judged the safety of glyphosate and Roundup. Conclusions from three major health organizations [Health Canada, United States Environmental Protection Agency (U.S. EPA), and World Health Organization (WHO)] are publicly available (Health and Welfare Canada, 1986, 1992; U.S. EPA, 1993, 1997a, 1998a; WHO 1994a). Those reviews, which have applied internationally accepted methods, principles, and procedures in toxicology, have discovered no grounds to suggest concern for human health." (pp. 118-119)*

Always read and follow use directions. Roundup is a registered trademark of Monsanto Technology LLC.

(November 2001)

Reference 3

"Summary of Ecotoxicological Risk Assessment for Roundup® Herbicide," Monsanto Company Backgrounder, November, 2001.

Backgrounder

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Summary of Ecotoxicological Risk Assessment for Roundup® Herbicide

Three internationally recognized experts in environmental toxicology have completed and published a peer-reviewed environmental safety evaluation of glyphosate and the basic Roundup herbicide formulation that has been used around the world for more than twenty years. This formulation contains the active ingredient glyphosate (as the isopropylamine salt), water and a surfactant (polyoxyethylenealkylamine or POEA).

The authors reviewed Monsanto studies that had been previously considered by regulatory authorities around the world. In addition, they reviewed reports from regulatory and scientific institutions as well as a wide array of studies conducted by independent researchers using information from the public literature. Over a two-year period, more than 250 documents were reviewed to evaluate the potential risk to wildlife (including mammals, birds, insects, soil invertebrates, microorganisms, fish, amphibians, and aquatic invertebrates) and to non-target vegetation.

The paper, "Ecotoxicological Risk Assessment for Roundup® Herbicide," by John P. Giesy, Stuart Dobson and Keith R. Solomon, was published in *Reviews of Environmental Contamination and Toxicology*, (2000) Volume 167, pages 35-120. The overall findings of this evaluation are described below.

Summary of Findings

The current state of knowledge on the ecological effects of Roundup® herbicide and its active ingredient glyphosate was reviewed. A comprehensive ecotoxicological risk assessment was conducted using a conservative hazard quotient method, in which a hazard quotient less than 1 indicates minimal risk of adverse effects. The no-effect-level for the most sensitive species was used as the toxicity endpoint in the assessment for aquatic and terrestrial organisms potentially exposed to Roundup or its components. Exposure levels were derived from environmental monitoring data or dissipation models. The predicted maximum acute and chronic hazard quotients were less than 1 for aquatic and terrestrial organisms following terrestrial Roundup uses, confirming that there is minimal risk of adverse effects. The acute assessment for honeybees also indicated minimal risk of adverse effects. Minimal risk of adverse effects was also indicated for beneficial arthropod populations in areas adjacent to treated areas. The authors concluded that expected vegetation change in treated areas can impact beneficial arthropod populations living there. The authors further concluded that Roundup use for aquatic habitat restoration can be conducted without unreasonable adverse effects on the environment, provided that factors such as application rate, depth of water, vegetation density, and overall rehabilitation goals are considered. This assessment indicates that application of Roundup in terrestrial and aquatic sites, including agriculture, forestry, residential, rights-of-way and habitat restoration, poses minimal risk to non-target species.

Key Findings:

- **Glyphosate readily dissipates from soil and water.** Glyphosate degrades to natural products such as carbon dioxide and phosphate ions. *"Field studies indicate that glyphosate typically dissipates rapidly from both simple ecosystems, such as agricultural, and more complex ecosystems, such as forestry..." (p. 51)* Glyphosate has been shown to degrade in terrestrial and aquatic systems predominantly via microbial processes. Field studies conducted in agricultural and forest soils (13 studies, 5 countries, 47 different sites) indicate an average half-life of 32 days. *"Both field and laboratory studies have reported microbial degradation of glyphosate to AMPA and CO_2 in aquatic environments and rapid dissipation from both flowing and standing surface waters."* (p.53).
  "The results of field studies indicate that 50% of the concentration of glyphosate initially found in water dissipates within time periods ranging from a few days to 2 weeks." (p. 53)

- **Contact with soil reduces bioavailability.** *"Once glyphosate enters the soil, it is essentially unavailable to plants due to its very high affinity for soil."* (p. 43)

- **Minimal leaching and runoff.** *"Although glyphosate is very soluble in water, its strong sorption to soils limits mobility."* (p. 48) *"Glyphosate is unlikely to leach into ground water or runoff significantly into surface water following application.* (p. 49) *"POEA* [the surfactant in Roundup] *strongly adsorbs to soil ... thus, the mobility of POEA in soil is expected to be less than 2%."* (p. 50)

- **Spray drift is well characterized.** *"Glyphosate has no significant vapor pressure; therefore, loss of glyphosate to the atmosphere via vaporization from treated surfaces is negligible."* (p.47) Spray drift can occur into non-target areas, but the drift levels have been well characterized. No adverse effects are predicted for animals or soil microbes as a result of aerial spray drift. Non-target plants directly adjacent to the treated fields may be affected if present at a sensitive life stage; however, no effects are predicted at distances greater than 4 m. *"Aerial applications can result in increased drift relative to ground applications, but recent technological advances have significantly reduced aerial spray drift."* (p. 103)

- **No bioaccumulation in animals.** *"Neither glyphosate nor Roundup would be expected to bioaccumulate."* (p. 57) *"...glyphosate does not bioconcentrate in fish or other animals."* (p. 103).

- **Terrestrial applications pose little risk to:**
  Aquatic organisms (including amphibians) – *"[Hazard Quotient] values are considerably less than 1.0, indicating that Roundup poses minimal risk to aquatic organisms following terrestrial use."* (p. 89) *"...minimal risk from the application of Roundup would be expected for sediment dwelling organisms."* (p. 89)
  Soil organisms – *"...minimal acute hazard is predicted for populations of soil organisms."* (p. 94) *"The weight of evidence for effects of Roundup on soil microorganisms indicates that adverse effects would be unlikely as a result of application at normal field rates ... Earthworms are predicted to be at minimal risk from the use of Roundup or glyphosate."* (p. 95-96)
  Beneficial arthropods (insects) – *"...the literature supports the conclusion that non-target arthropods are at minimal risk from glyphosate and its formulations."* (p. 99) *Most* effects result from habitat change because of the decision to remove vegetation. *"Several studies have found that the application of glyphosate can increase populations of beneficial insects ... No effects on the number of common butterfly species were observed when glyphosate was used to control trees, shrubs and blackberry in wire zones; but numbers of individuals did increase."* (p. 99) *"Honeybees are not affected by glyphosate formulations, either by ingestion or direct overspray, at maximum use rates."* (p. 103)
  Birds – *"Several comprehensive field studies have observed birds in forest plots treated with Roundup ... In no case was there evidence of direct toxicity of Roundup or glyphosate to birds."* (p. 97)
  Mammals – *"It has been concluded that there is minimal risk to small mammals from the application of glyphosate products and that the effects observed in the field studies are a result of changes in habitat."* (p. 98)

- **Aquatic applications help restore wildlife habitat.** *"Glyphosate has been used extensively to control aquatic weeds and restore ecosystems affected by introductions of exotic weeds."* (p. 101) The objective of an aquatic herbicide application is to remove weed species. *"It is inevitable that some short-term population level effects on plants and associated animals should occur in the pursuit of a long-term goal characteristic of restoration/rehabilitation projects."* (p. 100) Roundup[2] can be safely used for aquatic habitat restoration projects with knowledge of the water depth, vegetation density, and overall rehabilitation goal.

[1] *"Formulations of glyphosate, including Roundup® Herbicide, have been extensively investigated for their potential to produce adverse effects in non-target organisms. Governmental regulatory agencies, international organizations, and others have reviewed and assessed the available scientific data for glyphosate formulations, and independently judged their safety. Conclusions from three major organizations are publicly available and indicate Roundup can be used with minimal risk to the environment (Agriculture Canada 1991; United States Environmental Protection Agency (USEPA) 1993a; World Health Organization (WHO) 1994)." (p. 36)*

[2] The Roundup formulation is only labeled for aquatic use in certain world areas. Other glyphosate-based products are labeled for aquatic use in other world areas. Use of a product inconsistent with its label is a violation of law and is strictly prohibited.

REFERENCES IN ITALICS THROUGHOUT THIS DOCUMENT REFER TO STATEMENTS OR CONCEPTS EXPRESSED BY THE AUTHORS OF "ECOTOXICOLOGICAL RISK ASSESSMENT FOR ROUNDUP® HERBICIDE."

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(November 2001)

Always read and follow use directions. Roundup® is a registered trademark of Monsanto Technology LLC.

Reference 4

"Glyphosate and Standard Toxicology Studies," Monsanto Company Backgrounder, September, 2002.

MONSANTO

Backgrounder
Glyphosate and Standard Toxicology Studies
September 2002

Monsanto Company

Toxicology is the study of the harmful effects of substances on living organisms: humans, plants and animals. Toxicological testing evaluates the biological response of living organisms to different routes and durations of exposure to a substance. Modern toxicology contributes to clinical, legal, occupational and veterinary medicine and plays a key role in the development of drugs, food additives, home products, cosmetics, industrial chemicals, agrochemicals, pesticides, etc. Paracelsus, a 16th Century Swiss physician recognized as the "father of toxicology," is noted for his principle that all substances are poisons if the dose is sufficiently high – "the dose makes the poison." He understood that the relationship between dose and response are inseparable. At very low doses, even notorious toxins such as arsenic will not cause harm. Conversely, at very high doses, essential substances such as water will harm or kill.

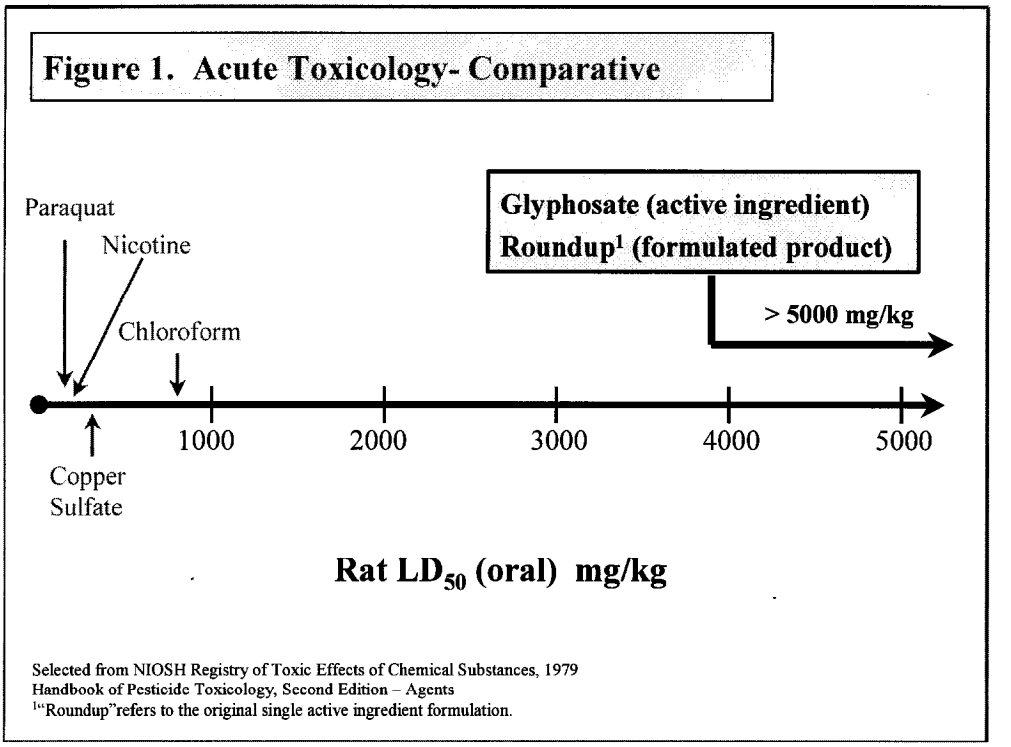
The story is no different for pesticides; at some dose they are harmful and at some dose they are harmless.

Pesticides (herbicides, insecticides, rodenticides, fungicides, etc.) cannot be categorized simply as "dangerous" just because they are classified as substances that kill pests. Likewise, no chemical, either natural (made by plants or other organisms) or synthetic (made by man), can be determined to be completely "safe." The study of toxicology determines what doses are harmful and what doses would not be expected to pose unreasonable risk. Pesticides are strictly regulated by governmental agencies around the world. In the United States, the U.S. Environmental Protection Agency has that responsibility and requires a battery of toxicological and environmental studies. On average, a pesticide active ingredient must undergo at least 120 tests before it can be registered for use. During the many years that glyphosate and glyphosate herbicides have been used, hundreds of toxicology studies have been conducted.

All pesticides are evaluated for acute, sub-chronic and chronic effects. Acute toxicological testing evaluates whether a single high-dose exposure to a substance will produce acute effects. (An acute effect could be anything from a skin rash to death.) Sub-chronic effects are related to several days or weeks of continuous exposure to a substance. Chronic effects occur after a long period (approaching a lifetime) of continuous exposure. Longer-term studies evaluate whether continual exposure to a substance has the potential to cause adverse effects, such as cancer, neurotoxicity, birth defects or reproductive problems.

Acute toxicity studies

Acute toxicity studies evaluate the risk from a single exposure to a substance, typically at a high dose. Acute oral and dermal toxicity studies are frequently designed to express the potency of a substance in terms of a median lethal dose or LD_{50}. The LD_{50} is the dose that is lethal to 50 percent of the laboratory animals in the test. The higher the LD_{50} value, the lower the toxicity. The dose is calculated as milligrams of the test substance per kilogram of body weight of the tested animals (mg/kg bw).



Laboratory studies show that glyphosate has acute rat oral and dermal LD_{50s} of greater than 5,000 mg/kg. The major use of the LD_{50} study is a comparative one, allowing an investigator to assess the relative toxicity of one substance with others tested in the same species (Figure 1). Accepted toxicology standards classify substances with an LD_{50} greater than 5,000 mg/kg as "practically non-toxic." (Remember, nothing can be considered *completely* non-toxic, because as Paracelsus knew, everything is toxic at some dose.)

In addition to acute rat oral and dermal studies, inhalation exposure also is evaluated to determine a spray concentration that is lethal to 50 percent of the test animals (LC_{50}). The dose is measured in milligrams of the test substance per liter of water (mg/L). Acute rat inhalation studies with glyphosate show that a high concentration is required to produce lethality.

The U.S. EPA places pesticides in one of four categories for acute toxicity, based on their LD_{50} and LC_{50} values. Category I is considered the most toxic, and category IV the least toxic. Glyphosate is assigned a Category IV ("practically non-toxic") for all three routes of exposure – oral, dermal and inhalation. Eye and skin irritation studies also are required to assess the potential for a substance to cause irritation. Glyphosate is assigned a Category IV for skin irritation. However because the technical material is an acid it can be moderately to severely irritating to the eyes. Glyphosate formulations are made not with the acid but with a salt of the acid. These salt solutions are considered practically non-irritating to the eyes and are assigned a Category IV. One other acute test is used to evaluate the potential of a pesticide to produce an allergic skin reaction after repeated skin contact. Glyphosate shows no evidence of causing a skin reaction.

Not only do the pesticide active ingredients undergo this battery of testing, but so does each product formulation containing the active ingredient. Most formulated herbicides in which

glyphosate is the active ingredient (e.g. Roundup UltraMAX® and Roundup Pro®) are also in Category IV for acute oral, dermal and inhalation toxicity.

Subchronic and chronic toxicity studies

The acute toxicity studies determine what dose is lethal to 50 percent of the test animals via a specific route of exposure, but they do not determine what dose poses no unreasonable risk. That determination is made by examining effects seen over a range of doses and durations of time. Sub-chronic studies last for a few weeks to months (~10 percent of the normal life span of the test animal), and chronic studies can last for a year or more (the expected lifetime of the test animal). Exposure routes are identical to those of acute testing programs (oral, dermal, inhalation). In sub-chronic and chronic oral toxicity studies, groups of test animals are given various daily doses, from zero to thousands of milligrams per kilogram of their body weight. At the end of a designated exposure period, virtually every organ system and physiological parameter is examined to determine any differences between exposed and non-exposed test animals. High doses must elicit sub-lethal effects, middle doses must evoke only minimal adverse effects and low doses should trigger no toxic effects whatsoever. Generally, three to five dose levels are tested. The highest tested dose level that produces no observed adverse effects is referred to as the NOAEL. Different toxicity studies produce different no-effect levels. The U.S. Environmental Protection Agency (EPA) bases its risk assessment on the lowest NOAEL recorded in the various studies. See the table below for a summary of NOAELs seen in various glyphosate toxicity studies submitted to the U.S. EPA.

Toxicity Study	**Glyphosate NOAEL (mg/kg/day)[1]**
Rat Subchronic	209
Rat Chronic	409
Rat Reproduction	694
Rabbit Developmental	175
U.S EPA - NOAEL	175

[1] Source: EPA, 1993

Between the NOAEL and the highest dose tested, there is usually a range of doses that produce a range of effects. Some effects can be quite serious, such as tumors or birth defects; others are minor and would be reversible with cessation of exposure. Through all of these studies, even very high sub-lethal doses of glyphosate have not produced effects such as cancer, birth defects, mutagenicity, neurotoxicity or reproductive abnormalities. Other effects, such as weight loss, elevated enzyme levels, etc. have been detected in those studies, almost always at very high doses. For example, in the rabbit developmental study, designed to determine if glyphosate causes adverse effects in pregnant animals and their developing offspring, no developmental effects were seen even at the highest dose which produced toxicity to the pregnant animal. The NOAEL for this study was considered to be the 175 mg dose. It was the lowest NOAEL from various studies.

Reference dose (RfD) includes uncertainty factors to reduce risk

After a NOAEL is determined the U.S. EPA applies uncertainty factors to account for differences between humans and test animals and individual variability. The agency also considers the types of effects that were seen at higher doses. Less serious effects normally constitute a lower margin of exposure. The margin for glyphosate has been set at 100-fold, as opposed to some other pesticides which have margins of exposure of 1,000 or more because of less favorable toxicological results. ***A 100-fold uncertainty factor means that acceptable human exposure for glyphosate has been established at a level that is 100 times lower than a tested dose that caused no observable adverse effect in tested animals.*** For glyphosate, the acceptable daily dietary exposure, referred to as reference dose (RfD) has been set at 2 mg/kg/day (175 mg/kg/day NOAEL divided by 100 = 1.75 mg/kg/day rounded up to 2 mg/kg/day).

In 1996, Congress unanimously passed landmark pesticide food safety legislation called the Food Quality Protection Act (FQPA). The FQPA mandated that allowable exposure levels more closely consider infants and children. The FQPA required the U.S. EPA to apply an additional 10-fold uncertainty factor to account for exposure to children, who have higher relative exposure because of their lower body weight. However, EPA was given the option of applying a lesser uncertainty factor "only if, on the basis of reliable data, such margin will be safe for infants and children" (FQPA, 1996). The additional uncertainty factor, when applied to the RfD, yields an exposure level called the chronic Population Adjusted Dose (cPAD).

EPA reviewed the toxicological database for glyphosate, determined that it was complete and concluded there was no indication of increased sensitivity to glyphosate among infants and children. Therefore, EPA used an FQPA uncertainty factor of 1, resulting in a cPAD for glyphosate of 2 mg/kg/day, the same as the RfD.

Calculating human exposure

In order to calculate human exposure to a pesticide, the U.S. EPA considers all possible routes, including food, water, applicator exposure, or bystander exposure from drift. Conservative assumptions are made throughout the process. Consider exposure through food, for example. EPA requires food residue studies for every crop on which a pesticide is to be used. For the study, the pesticide is applied at the maximum labeled rate. (Most farmers use rates much lower than the maximum allowed.) Crops are harvested and liquefied, and very sensitive equipment is used to seek traces of the pesticide. Multiple samples are taken from several test plots grown in various geographic regions. The sample with the highest amount of residue is recorded for the crop in question, even if some unusual condition may have been at play. If no residue is detected in any of the samples, EPA assumes a presence anyway. Based on these studies, EPA calculates how much residue could be present in crops treated with the pesticide. It is then assumed that every acre of every crop for which the pesticide is labeled receives an application of the pesticide (with no allowance for market share). Furthermore, EPA assumes that people consume every crop every day. (Glyphosate is labeled for use on more than 100 crops, so this is a very conservative assumption.) If adding up the residues from each crop yields a dose greater than the EPA's cPAD, the public is assumed to be at risk and some uses must be discontinued in order to reduce public exposure.

In September 2000, EPA approved a new crop use for glyphosate. At that time, the agency concluded that even non-nursing infants, whose food consumption relative to body weight is higher than adults, were exposed to no more than 3.2 percent of the allowable dose through food (U.S. EPA 2000).

Wildlife toxicology

In addition to many studies with laboratory animals to assess potential effects from human exposure, glyphosate has also been studied to determine effects on wildlife. The same toxicological principles apply – varying doses are given to representative species of birds, fish, insects and other invertebrates. The lethal dose or concentration is determined, and effects seen at lower doses are examined. A no-effect level is also determined. These studies show that glyphosate has very low toxicity to wildlife and that expected exposure from approved uses of glyphosate products would pose no unreasonable risk to wildlife.

Related Document:

Backgrounder: Glyphosate and Wildlife. December, 2002.

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Reference 5

"Glyphosate and Environmental Fate Studies," Monsanto Company Backgrounder, April, 2003.

MONSANTO

Backgrounder
Glyphosate and Environmental Fate Studies
April 2003

Monsanto Company

Before a herbicide can be registered for use, it must undergo rigorous studies to determine what happens to the compound after it is released into the environment, either from an intended use or an accidental release, such as a spill. These studies, referred to as "environmental fate" studies, are reviewed by the U.S. Environmental Protection Agency (EPA) and regulators in other world areas and are designed to provide answers to the following questions:

Does the herbicide:

- degrade after application? If so, what degradation products are formed after application?
- persist in soil?
- have residual herbicidal activity in soil?
- persist in water or sediment?
- leach through soil to reach groundwater?
- move from treated areas as runoff?
- move from treated areas as a vapor?
- accumulate in tissues of animals?

Laboratory and field studies have been conducted with glyphosate and glyphosate herbicides (such as Roundup UltraMax, Roundup Pro, and AquaMaster™) to address these questions. The overall results of these environmental fate studies are summarized below

Degradation processes and products

The processes by which a herbicide is degraded must be understood before the U.S. EPA and other regulatory agencies will register the herbicide. Some products break down by chemical processes, others through photodegradation, and others by microbial activity or a combination of several processes. Glyphosate is primarily degraded by microbes and fungi in the soil or in water, under both aerobic (in the presence of oxygen) and anaerobic (in the absence of oxygen) conditions. Photodegradation in water and soil are not expected to contribute significantly to glyphosate degradation.

The identity and characteristics of the compounds that are formed as a herbicide degrades must also be determined. The primary environmental degradate of glyphosate in soil and water is aminomethylphosphonic acid (AMPA). AMPA is also a degradate of other chemicals, such as phosphonate-containing detergents (Steber and Wierich 1987). AMPA is further degraded to naturally-occurring substances such as carbon dioxide and phosphate. Acute oral and dermal toxicity studies with rats and mice in the laboratory demonstrate that AMPA has very low acute toxicity to mammals (Williams *et al.*, 2000). A number of ecotoxicology studies have been conducted to assess AMPA's toxicity to aquatic and terrestrial species. Based on the results, AMPA can be characterized as having little toxicity to non-target organisms (Giesy *et al.*, 2000).

Degradation in soil

Studies must also be performed to determine how much of the herbicide would be expected to remain in soil following normal use, and the rate of degradation. Research shows that

glyphosate is degraded over time by soil microorganisms. The degradation rate of chemical compounds is measured by their half-life (the time required for half of the applied compound to degrade). The average half-life for glyphosate, based on 47 agricultural and forestry studies conducted in many geographic locales, is 32 days (Giesy *et al.*, 2000). In most cases, over 90% of the applied glyphosate will be degraded within six months after application.

Binding to soil

Glyphosate binds very tightly to most soils and sediments in the environment. Studies show that the soil-binding potential of glyphosate is stronger than that of nearly any other herbicide. A ratio known as the "soil adsorption coefficient" (Koc) measures the soil-binding capacity of chemical compounds, with higher numbers meaning greater adsorption of the compound to soil.

The following table shows representative Koc values for several herbicides, as reported by the USDA Soil Conservation Service:

Active ingredient	Koc value
2,4-D	109
Alachlor	170
Metolachlor	200
Trifluralin	7,000
Glyphosate	24,000
Pendimethalin	24,300

Herbicidal activity of residues in soil

Because of its strong soil-binding properties in most soils, glyphosate is not available for uptake by roots of nearby plants, and therefore poses negligible risk to non-target plants with roots in the application zone. Further evidence of this is provided by the fact that even susceptible, conventional crops may be planted directly into fields that were recently treated with a glyphosate herbicide. Studies also show that glyphosate herbicides, when used according to label directions, are not harmful to soil microbes, earthworms or other soil-dwelling organisms (Giesy *et al.*, 2000).

Degradation in water

Both field and laboratory studies have reported microbial degradation of glyphosate in aquatic environments (Giesy *et al.*, 2000). Analysis of available data representing many studies indicates that the typical aquatic half-life of glyphosate ranges from 7 to 14 days . Studies have established that microorganisms in surface waters break down glyphosate over time. Also, because of its strong affinity for soil, glyphosate binds to suspended sediment particles that are present in natural waters. As the particles settle to the bottom, microbial degradation continues. Toxicology studies show that glyphosate levels that might occasionally be detected in surface waters following terrestrial application are sufficiently low so that there is negligible risk to aquatic organisms. In situations where a glyphosate herbicide is applied to weeds growing in water, the exposure of non-target aquatic species may be reduced due to interception by target vegetation and dissipation over time via binding to sediment and microbial degradation.

Leaching and runoff

Two primary factors determine whether a chemical is likely to leach through soil to groundwater or be subject to movement into surface water via runoff -- the rate of degradation in the soil, and the chemical's tendency to bind to soil. Slow degradation and a low tendency to bind to soil can

result in leaching and runoff of a chemical, whereas higher degradation rates and tight binding to soil both limit the movement of a chemical by leaching and runoff.

With its combination of degradability and tight binding to soil, glyphosate has extremely low potential to move through the soil profile and has rarely been detected in groundwater. In addition, only limited amounts of glyphosate move to surface water as runoff. A three-year study of glyphosate transport from agricultural fields showed that less than 1 percent of glyphosate applied was typically lost as runoff; In one case, a loss of 1.85 percent of applied glyphosate was observed for a field treated at twice the recommended application rate, with more than 99 percent of the total runoff occurring during a severe rainstorm that occurred the day after application (Edwards *et al.*, 1980). If soil particles containing glyphosate are washed or blown into lakes or streams, the vast majority of the glyphosate will remain adsorbed to the soil and settle to the bottom as sediment. In sediment, glyphosate is degraded over time by microorganisms. Studies also show that sediment-dwelling organisms are not adversely affected by glyphosate (Simenstad *et al.*, 1996).

Bioaccumulation

Aquatic Species: In laboratory studies conducted with several aquatic species, glyphosate bioconcentration factors were less than or equal to 12, indicating that glyphosate has a low potential for bioaccumulation in aquatic animals (Giesy *et al.*, 2000). The low bioconcentration factors are a result of glyphosate being readily soluble in water, and therefore subject to rapid elimination from organisms in water.

Terrestrial Species: Studies conducted with laboratory mammals indicate that glyphosate is poorly absorbed when ingested; any absorbed glyphosate is rapidly eliminated, resulting in minimal tissue retention (Williams *et al.*, 2000). Feeding studies with chickens, cows and pigs have shown extremely low or non-detectable residues in meat and fat following repeated exposures. Negligible residues have also been reported in wild animals such as voles, chipmunks, hares and moose after feeding in treated areas.

Vapor and drift

The active ingredients in some herbicides are volatile, meaning that they can move as vapors to non-target areas after application. This can result in unintended consequences to sensitive plant species outside the treated area. Several laboratory studies show that glyphosate has extremely low vapor pressure and thus there is a negligible risk of glyphosate movement through volatility (Giesy *et al.*, 2000).

However, it is possible, as with any sprayed substance, that spray droplets could drift off-target during application. Research has demonstrated that application procedures and equipment can be optimized to significantly reduce spray drift in most circumstances. Spray drift can be minimized by taking into account spray droplet size, wind speed, other environmental factors and application equipment design. When drift does occur, there is a rapid decline in surface deposition with increasing distance from the target site for both ground and aerial applications.

Conclusions

The key properties of glyphosate that determine glyphosate's environmental fate are its:

- Microbial degradability in soil and water
- Tight binding to most soil types
- High water solubility
- Very low volatility

Glyphosate is microbially degraded over time to naturally occurring substances. There is minimal herbicidal activity from residues of glyphosate in soil, and glyphosate residues are not likely to move to groundwater. Glyphosate that reaches surface water either by intentional application, spray drift, runoff, or soil erosion is adsorbed to sediment and degraded over time. Glyphosate is unlikely to move offsite during or after application due to volatilization. Available data indicate that glyphosate is not likely to bioaccumulate in the tissues of non-target organisms.

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Related Documents:

- Backgrounder: Authoritative Sources for Glyphosate Information
- Backgrounder: Glyphosate Half-life in Soil
- Backgrounder: Glyphosate and Drift
- Backgrounder: Glyphosate and Water Quality
- Backgrounder: Formaldehyde is not a degradate of glyphosate