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

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MAR 1 1986

Caswell 661A

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate Registration Standard Revision

TO: Robert Taylor (25)
Herbicide-Fungicide Branch
Registration Division (TS-767)

FROM: D. Stephen Saunders Jr., Ph.D.
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TOX/HED (TS-769)

DSS 2/28/86
FDC 2/28/86

THRU: Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Theodore M. Farber
3/1/86

Attached is a revised version of the Toxicology Chapter for the Glyphosate Registration Standard. Included are the following:

1. A revised review of toxicity data for Glyphosate which reflects the SAP interpretation of the mouse oncogenicity data, and the recent submission of a chronic dog study. The bibliography has also been appropriately revised.

2. Updated TOX "one-liners". Page 3 of the glyphosate one-liners (Caswell #661A) should be replaced by the revised page 3, which is appended.

3. Revised Tolerance Assessment.

The "Phase II Data Tables" should be updated to reflect the submission of the dog study, and the requirement for a repeat mouse oncogenicity study.

Needs document # - No entry made

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Acute Toxicity

Acute oral and dermal toxicity data (Birch, 1970, MRID #00067039) place technical glyphosate in Toxicity Category III. Primary eye and skin irritation data (Birch, 1970, MRID #00067039) indicate that technical glyphosate is not a primary skin irritant (Toxicity Category IV), and is only minimally irritating to the eye (Toxicity Category III). An acute inhalation study for the technical grade of active ingredient (TGAI) has not been submitted and is required. A dermal sensitization study on the TGAI has not been submitted and is required.

Chronic/Oncogenicity

Glyphosate produced an equivocal oncogenic response in the mouse (Knezevich and Hogan, 1983), causing a slight increase in the incidence of renal tubular adenomas (a benign tumor of the kidney) in males at the highest dose tested of 30,000 ppm. These data were reviewed by the Toxicology Branch Oncogenicity Peer Review Committee which concluded that the study demonstrated a weak oncogenic response. The slides were re-examined by a consulting pathologist, and data were submitted indicating that an additional kidney tumor had been found in control males (no renal tumors were found in controls in the original examination). The Agency then requested that additional kidney sections from the mouse study be prepared and examined. The resultant microslides were examined by a number of pathologists, including Dr. Louis Kasza of Toxicology Branch. These examinations revealed no additional tumors, but confirmed the presence of the tumors identified in the original study report. The apparent lesion in the control kidney was not present in any of the additional sections. After examination of the slides, Dr. Kasza concluded that this lesion did not "represent a pathophysiologically significant change".

These data were presented before the FIFRA Science Advisory Panel (SAP), which was asked to provide an assessment of the proper weight of the evidence classification of the oncogenic potential of glyphosate. After reviewing all available data, the SAP concluded that the data were equivocal, and a clear designation of the oncogenic potential of glyphosate was not possible based on available data. The SAP proposed that glyphosate be categorized as Class D, and "that there be a data-call-in for further studies in rats and/or mice to clarify unresolved questions". The Agency has determined that the existing mouse study does not provide sufficient evidence for a resolution of this issue. Therefore, a repeat mouse study is required. The Registrant should submit a study protocol to the Agency prior to initiation of a new study.

Other non-neoplastic changes noted in high dose male mice included centrilobular hypertrophy and necrosis of hepatocytes, chronic interstitial nephritis, and proximal tubule epithelial cell basophilia and hypertrophy in females. The NOEL for non-neoplastic chronic effects was the mid dose, 5,000 ppm. This study is classified as Core-Minimum data.

The lifetime feeding study in rats (Lankas and Hogan, 1981, MRID 00093879) tested dietary concentrations of glyphosate of 0, 30, 100, and 300 ppm. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats were maintained. Thus, the doses tested in the rat chronic study were about 1/100 of those tested in the mouse study. Although no effect of treatment on the incidence of non-neoplastic lesions was noted, a marginal increase in the incidence of interstitial cell tumors of the testes was observed. It was concluded that the observed increase, although slightly higher in incidence than historical controls, was insufficiently large to demonstrate an oncogenic potential. An independent review of the data raised a question of possible thyroid carcinoma in high dose females. After a review of the slides by a consulting pathologist, the Agency concluded that the data did not demonstrate a carcinogenic response in the thyroid.

However, in view of the large difference in doses between the rat and mouse studies, the Oncogenicity Peer Review Committee speculated that "a toxic, or MTD [Maximally Tolerated Dose], was not reached in [the rat] study", and that at doses "close to an MTD, tumors might have been induced". The rat study was re-reviewed for evidence that the highest dose tested was an MTD. No effect of treatment on survival, body weight gain, clinical pathology, or findings at necropsy was noted. Therefore, there is no evidence that the highest dose tested was an MTD. A repeat rat study is required in which the highest dose tested is an MTD. This study is now re-classified as Core-Supplementary data for oncogenicity, and as Core-Minimum data for chronic effects.

A 1-year chronic feeding study in dogs (Reyna and Ruecker, 1985) tested doses of 0, 20, 100 and 500 mg/kg/day, administered by capsule. The only effect of treatment was an apparent decrease in the absolute and relative weights of pituitaries from mid and high dose dogs. However, the Registrant has been requested to provide additional data in order to better assess this apparent effect. The NOEL for this effect has been tentatively established as 20 mg/kg/day, and the study is tentatively classified as Core-Guideline data pending the submission of additional data.

Subchronic Toxicity Studies

No acceptable rat or dog subchronic feeding studies are available for technical glyphosate. IBT studies had been submitted for both species, however were found to be invalid.

A 3-month subchronic study in mice (Street et al., 1980, MRID #00036803) tested dietary concentrations of 0, 5000, 10000, and 50000 ppm of technical glyphosate. A decrease in body weight gain was noted in high dose mice, however no gross or microscopic changes were observed at necropsy. The study was classified as Core-Supplementary data because hematology, clinical chemistry, and urinalysis measurements were not performed.

A 21-day dermal toxicity study in rabbits tested dermal doses of 100, 1000, and 5000 mg/kg/day for 5 days/week for three weeks (Johnson, 1982). The only effect noted was slight edema and erythema of the skin at the high dose (5000 mg/kg/day). The NOEL for these effects was 1000 mg/kg/day, and the study was classified as Core-Minimum data.

Teratology and Reproduction

Acceptable rabbit (Rodwell et al., 1980, MRID #00046363) and rat (Rodwell et al., 1980a, MRID #00046362) teratology studies have been submitted. No evidence of teratogenicity was observed in either study. In the rat study, evidence of developmental toxicity in the form of unossified sternebrae was noted in fetuses from high dose (3500 mg/kg/day) dams. This dose was also toxic to dams as evidenced by weight gain deficits, altered physical appearance, and mortality during treatment. The NOEL for developmental and maternal toxicity was 1000 mg/kg/day, and the study was classified as Core-Minimum data.

In the rabbit study, the highest dose tested (350 mg/kg/day) was toxic to does as evidenced by altered physical appearance and mortality. In spite of the toxicity of the high dose, no treatment-related fetal effects were noted. The NOEL for maternal toxicity was 175 mg/kg/day, and the study was classified as Core-Minimum data.

In the three-generation rat reproduction study (Street, 1981) and addendum (Street et al., 1982) the most significant finding was focal, unilateral, renal tubular dilation in the kidneys of male pups from the F_{3b} generation of high dose dams (30 mg/kg/day). The NOEL for this effect was 10 mg/kg/day. No effects on fertility or reproductive parameters were noted. The study was classified as Core-Minimum data.

Mutagenicity

Acceptable studies have been submitted to satisfy the Agency's testing requirements for gene mutations, chromosomal aberrations, and primary DNA damage. Glyphosate was negative for gene mutations in chinese hamster ovary cells (Li et al., 1983) in the presence or absence of microsomal activation. Glyphosate was also negative for gene mutations in bacteria, with or without activation (Inst. of Env. Tox. [Tokyo], 1978; Monsanto Env. Health Labs. #LF-78-161, 1978). Glyphosate was negative for chromosomal aberrations in the mouse dominant lethal test (Rodwell et al., 1980b, MRID #00046364), and in the in vivo cytogenetics assay (Li, 1983; Ridley, 1983). No primary DNA effects were seen with glyphosate in the B. subtilis rec assay (Inst. of Env. Tox. [Tokyo], 1978) or in the rat hepatocyte DNA repair assay (Williams, 1983).

Neurotoxicity

Even though glyphosate is not a typical organophosphate, a delayed neurotoxicity study was conducted in chickens at Industrial Bio-Test Laboratories (Fletcher and Arceo, 1976, MRID #00054494). Although no evidence of neurotoxicity was noted in the study, the validation report for this study noted an absence of raw data for dose preparation and administration, body weight measurements, and pathological observations for untreated and positive control birds. After evaluation of the study for scientific content, the study was classified as invalid on the basis of the extensive gaps in the raw data supporting study findings and conclusions.

Since glyphosate is not an organophosphate insecticide, a repeat study is not required.

Metabolism

Available metabolism data (Colvin et al., 1973; Colvin et al., 1973a) demonstrate that glyphosate is rapidly excreted by rats, as >90% of the administered dose was eliminated within 48 hours of treatment. In males, the majority of excretion was via the feces (80%), and about 15% of the administered dose was eliminated in the urine. In females, about 40% of the administered dose was excreted in the urine, which suggests that female rats absorbed more glyphosate from the gastrointestinal tract than did males.

After a single oral or intraperitoneal dose less than 1% of the administered dose was retained at 120 hours after treatment. In animals fed 1, 10 or 100 ppm of ^{14}C-glyphosate for 14 days, a steady-state equilibrium between intake and excretion of label was reached within about 8 days. The amount of radioactivity excreted in the urine declined rapidly after withdrawal of treatment. By 10 days after withdrawal, detectable levels of radioactivity were measured in the urine and feces of only the rats fed 10 or 100 ppm of the test diet. Only minimal residues of 0.1 ppm or less remained in the tissues of high dose rats after 10 days of withdrawal, with no single tissue showing a significant difference in the amount of label retained.

The submitted studies are deficient in that data for the analysis of excreta for the presence of metabolites were not submitted, and only 1-3 animals were used in each experimental group. The submitted data demonstrated differential effects on excretion and retention of radioactivity depending on the molecular location of the radioactive label. These findings are strong evidence that some metabolism of glyphosate occurred in rats.

The metabolism studies for glyphosate are classified as Core-Supplementary data, and repeat studies are required.

N-Nitroso-Glyphosate

Residue Chemistry Branch (RCB) has determined that technical glyphosate contains N-nitroso-glyphosate (NNG) as a contaminant at levels of 0.1 ppm or less. Current policy on nitroso contaminants is that oncogenicity testing for these contaminants will normally be considered only in those cases in which the level of nitroso compounds exceeds 1.0 ppm. Therefore, although a chronic feeding study in rats was reviewed and found unacceptable, no additional studies are requested at this time.

Acute oral toxicity data for NNG (Younger Labs., 1975; ibid, 1976) place it in Toxicity Category III. Other acute toxicity data for NNG are not available in Toxicology Branch files.

Chronic toxicity studies in the dog and rat were conducted at IBT. After a raw data audit, both studies were judged to be Supplementary data. Both studies were then evaluated for scientific acceptability, and the rat study (Morrow et al., 1979) was classified as Core-Invalid due to dosing of the control groups with an excessive amount of NaCl which resulted in high mortality of control animals. The dog study (Jenkins et al., 1979) remained Core-Supplementary after scientific evaluation due to the lack of supporting raw data as identified in the raw data audit validation report. The only apparent treatment-related findings in the dog study were an increase in absolute and relative kidney weights and in blood glucose in high dose (30 mg/kg/day) females. The NOEL for this apparent effect was 10 mg/kg/day.

A 90-day subchronic oral toxicity study with NNG was conducted in the rat (Pharmacopathics Research Labs., 1982). The principal effect of treatment was a dose-related decrease in survival, food consumption and body weight gain. A NOEL was not established in this study since these effects were noted at the lowest dose tested, 3000 mg/kg/day. The study was classified as Supplementary data due to inadequate reporting of clinical sign and necropsy data, and inadequate identification of the test material.

A rat metabolism study conducted with NNG (Sutherland, 1978) demonstrated that NNG is rapidly absorbed and excreted, with the kidneys the preferential route of elimination. These findings are in direct contrast with the results of the metabolism studies with glyphosate, which found that absorption from the gut was poor and the majority of excretion occurred in the feces due to unabsorbed radiolabel. Tissue residues after 5 consecutive doses were minimal, as no tissue contained more than 1.5 ppm of radiolabel.

No acceptable studies for mutagenic or reproductive effects are available at present for NNG.

Plant Metabolite- Aminomethylphosphonic Acid

Residue Chemistry Branch has determined that the metabolite aminomethylphosphonic acid (AMPA) is formed on plants in amounts that can range as high as 28% of the total residue on the plant. Since the extent of glyphosate metabolism was not adequately addressed in the rat metabolism study, the possibility exists that the AMPA metabolite could pose a hazard to humans that was not evaluated by testing the parent compound, glyphosate. If an acceptable rat metabolism study is submitted which demonstrates significant conversion in animals of glyphosate to AMPA, additional studies on this metabolite may be unnecessary.

Acute oral toxicity and primary skin irritation data place AMPA in toxicity category IV (Birch, 1973, MRID 0008412[illegible]). The primary eye irritation study demonstrated that AMPA was slightly irritating to the eye, corresponding to toxicity category III (ibid).

A 90-day subchronic feeding study was submitted (Street, et al., 1979) that demonstrated irritation of the urinary bladder in rats treated with 1200 mg/kg/day, the LEL in this study. This irritation was manifested in the form of hyperplasia of the cells lining the bladder, and was noted with increased incidence and severity at the highest dose tested, 4800 mg/kg/day. Epithelial hyperplasia of the renal pelvis was also noted in high dose rats. The NOEL for this effect was 400 mg/kg/day, and the study was classified as Core-Minimum data.

A rat metabolism study (Colvin et al., 1973b) demonstrated that AMPA is rapidly excreted as the parent compound. No evidence for bioaccumulation was noted in this study, which was classified as Supplementary data because the number of animals studied was not reported, only males were studied, and the effects of a minimally toxic dose and repeated non-toxic doses on excretion, metabolism, and accumulation were not assessed.

The limited data available for AMPA do not suggest that this compound poses any hazard distinct from that of the parent compound. No studies are available by which to assess potential mutagenic, reproductive, oncogenic, or chronic effects of AMPA. The need for additional testing of this compound will be assessed after the submission of an acceptable rat metabolism study with glyphosate.

Tolerance Assessment

The Acceptable Daily Intake (ADI) for glyphosate is currently based on the finding of renal tubular dilatation in F_{3b} pups in the rat three generation reproduction study. The NOEL for this effect was 10 mg/kg/day. Using a 100-fold safety factor, the ADI for glyphosate is therefore 0.1 mg/kg/day, which is equivalent to a Maximum Permissible Intake of 6.0 mg/day in a 60 kg individual. Existing tolerances produce a Theoretical Maximum Residue Contribution (TMRC) of 1.4238 mg/day from a 1.5 kg diet, which occupies

$$\frac{1.4238 \text{ mg/day}}{6.0 \text{ mg/day}} \times 100 = 23.73\% \text{ of the ADI.}$$

Since the mouse oncogenicity study was equivocal, and has been classified as "Category D" according to the Cancer Assessment Group Guidelines, the possible findings in the mouse were not considered in the tolerance assessment for glyphosate.

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Tox Chem No. 661A - Glyphosate

Study/Lab/Study #/Date	Material	EPA Accession No.	Results/LD50, LC50, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2 Year feeding/oncogenic - rat; IBT; B-564, BTL 71-32; 1/14/74	Technical	112789	IBT-invalid		000265 000262 000280
2-Year feeding - dog; IBT;#J-565 (651-00565), BTL 71-33; 11/30/73	Technical (CP 67573 Acid form)	112789 94161	Evaluation considering Canadian validation findings of 6/19/78 and additional data submitted by Monsanto on 7/2/82 and reclassified as IBT invalid		000265 000269 002134
26 month feeding - rat; Bio/dynamic; #77-2062; 9/18/81	Technical 98.7% a.i.	246617 to 246621	Oncogenic NOEL > 31 mg/kg/day (HDT) Sys NOEL > 31 mg/kg/day (HDT) Supplementary for oncogenicity because MTD was not reached in this study. Minimum for chronic toxicity.		Minimum 001425 002175 002666 Supplementary (for onco) Minimum (for chronic) 004465
1-year feeding- dog; Monsanto Env. Health Labs.; #830116; 3/22/85	Technical 96.2% a.i.	260021	Doses: 0, 20, 100 and 500 mg/kg/day Systemic NOEL = 20 mg/kg (increased absolute and relative pituitary weights). Additional data requested from registrant. NOEL is tentative.		Guideline (tentative)
Neurotoxicity - hen;IBT; 8580-09117; 12/22/76	Technical		IBT valid per Canadian validation. Invalid per scientific evaluation.		000279 Invalid 004465
Mutagenic - gene mutation, CHO/HGPRT; Monsanto; #ML-83-155; 10/20/83	Technical	251737	Not mutagenic with or without S-9 activation		Acceptable 003868
Mutagenic - DNA repair (Rat hepatocytes); Monsanto; AH-83-181; 10/21/83	Glyphosate Technical	251737	Negative for DNA damage at concentrations between 1.25×10^{-5} and 1.25×10^{-1} mg/ml.		Acceptable 003868