



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

SEP 30 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: SECOND RfD/Peer Review Report of Sulfosate [N-phosphonomethyl - glycinetrimethylsulfonium salt].

CASRN. 81591-83-3
EPA Chem. Code: 128501
Caswell No. 893C

FROM: George Z. Ghali, Ph.D. *G. Ghali*
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (7509C)

THRU: William Burnam *W. Burnam*
Co-Chair, RfD/Peer Review Committee
Health Effects Division (7509C)

Reto Engler, PhD *R. Engler*
Co-Chair, RfD/Peer Review Committee
Health Effects Division (7509C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (7505C)

In the meeting of the Health Effects Division RfD/Peer Review Committee on March 10, 1994, the Committee recommended that neurotoxicity battery including acute neurotoxicity (81-8), subchronic neurotoxicity (82-7), and delayed neurotoxicity (81-7) be submitted with subsequent requirement of developmental neurotoxicity study if the outcome of these study warrants such data. This recommendation was based on the following observations: 1) increased incidence of white matter and nerve-root degeneration in lumbar region of spinal cord of male mice at the high dose tested (8000 ppm) and a compound-related increase in sciatic nerve degeneration at all dose levels in male mice in the two-year mouse study, 2) the observation of occasional sciatic nerve degeneration in male and female rats administered sulfosate topically at the rate of 1 gm/kg for three weeks, 3) the observation of hydrocephalus after one year of oral administration of sulfosate in dogs, and 4) the observation of lateral ventricle dilation in female dogs fed test compound at the rate of 50 mg/kg/day for three months.



The Committee was informed that the neurotoxicity studies have already been requested. Subsequently, these studies were submitted to the Agency for review. The first two studies were considered by the scientific reviewer to be acceptable as Guideline data and the third study was considered to be acceptable as Core-minimum data. Based upon the findings of these studies, the respective branch would determine whether a developmental neurotoxicity study would be required (RfD Peer Review report, July 26, 1994).

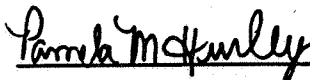
On August 11, 1994 the Committee reconvened to evaluate the neurotoxicity studies on Sulfosate and to determine whether or not the chemical is neurotoxic. Material available for review consisted of an acute delayed neurotoxicity study in hens (81-7), an acute mammalian neurotoxicity study in rats (81-8), and a subchronic neurotoxicity study in rats (82-7). The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the studies. After comprehensive evaluation of these additional data, the Committee concluded that: 1) the chemical was not associated with delayed neurotoxicity in the non-mammalian testing systems, 2) although some potentially positive findings were reported, there was no clear evidence of neurotoxicity, and 3) developmental neurotoxicity studies are not warranted.

Individuals in Attendance

Peer Review Committee members and associates present were William Burnam (Chief, SAB, Co-chair), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Marcia Van Gemert (Chief, TB II), Henry Spencer, William Sette and James Rowe. In attendance also was Linnea Hansen (non-committee member) as an observer.

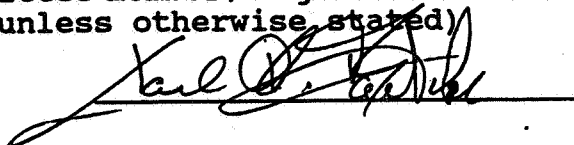
Scientific reviewer (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Pam Hurley



Respective branch chief (Committee member; Signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke



CC: Richard Schmitt
Stephanie Irene
Karl Baetcke
Pam Hurley
Debra Edwards
Kerry Dearfield
Beth Doyle
RfD File
Caswell File

Material Reviewed

Material available for review consisted of an acute delayed neurotoxicity study in hens (81-7), an acute mammalian neurotoxicity study in rats (81-8), and a subchronic neurotoxicity study in rats (82-7).

1. Mutter, L. C. (1989). Acute delayed neurotoxicity of ICIA-0224. MRID No. 43151201, HED Doc. No. 000000. Classification: Core-minimum data. This study satisfies data requirement 81-7 of Subpart F of the Pesticide Assessment Guideline for acute delayed neurotoxicity testing in hens.
2. Horner, S. A. (1993). Glyphosate trimesium: acute neurotoxicity study in rats. Classification: Guideline data. MRID No. 43132301, HED Doc. No. 000000. This study satisfies data requirement 81-8 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in rats.
3. Horner, S. A. (1993). Glyphosate trimesium: subchronic neurotoxicity study in rats. Classification: Guideline data. MRID No. 43151202, HED Doc. No. 000000. This study satisfies data requirement 82-7 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in rats.
4. Horner S. A. (1992). Measurement of motor activity in the rat. MRID No. 43013303, HED Doc. No. 000000 (a positive control study for assessment of motor activity in rats using amphetamine sulphate or chlorpromazine hydrochloride).
5. Allen, S. L. (1992). Assessment of muscular weakness in the rat. MRID No. 43013301, HED Doc. No. 000000 (a positive control study for assessment of muscular weakness in the rat using chlordiazepoxide).
6. Allen, S. L. (1992). Assessment of sensory perception in the rat. MRID No. 43013302, HED Doc. No. 000000 (positive control study for assessment of sensory perception in the rat using morphine sulphate).
7. Allen, S. L. (1992). Trimethyltin chloride; Neurotoxicity study in rats. MRID No. 43013304, HED Doc. No. 000000 (a positive control study: subchronic neurotoxicity in the rat using trimethyltin chloride).
8. Stonard, M. D. (1990). Acrylamide: Neurotoxicity study in rats. MRID No. 43013305, HED Doc. No. 000000 (a positive control study: subchronic neurotoxicity study in the rat using acrylamide).

NOTE

TO: George Ghali

FROM: Bill Sette *Bill 9/20/94*

RE: Sulfosate RfD writeup 9/6/94

I have 2 comments on this draft as written.

This meeting's purpose as I understood it was both to decide on a recommendation on a developmental neurotoxicity study and to evaluate the data reviewed in the acute hen, acute and 90 day rat neurotoxicity studies. The evidence of neurotoxicity cited in the other studies, i.e., a variety of neuropathological changes seen mostly in chronic studies in mice, rats, and dogs, and noted in the first paragraph of your memo were not presented or discussed at the August meeting. So, I think that the Committee should limit its conclusions in this memo about the neurotoxicity of this material to evaluation of the studies at hand.

I would also like to take issue with the first conclusion with respect to the findings concerning forelimb grip strength for the record. This I will do in a minority report forthwith.

Specifically, I ask that you modify the last sentence of the memo to read:

"After evaluation of these 3 studies [rather than comprehensive evaluation],
...2) although some positive findings were reported, which one committee member found of potential neurotoxicological significance, the Committee concluded that there was no clear evidence of neurotoxicity seen in these studies,".



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MEMORANDUM

SUBJECT: Sulfosate RfD Report: Minority Opinion on Significance of Certain Functional Effects seen in Rat Studies

TO: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (7509C)

FROM: William F. Sette, Ph.D.
Peer Review Section (7509C)
Science Analysis Branch

William F Sette
9/20/94

The purpose of this memo is to object to the conclusion of the RfD Committee regarding the lack of neurotoxic effects in acute and 90 day neurotoxicity studies of Sulfosate. Specifically, in my view, the effects on forelimb grip strength noted in both acute and the 90 day study not only were adverse and treatment related, but may be related to nervous system function. Thus, I feel it is inappropriate to conclude that a neurotoxic action as the source of these effects is either unlikely or can be ruled out. This has no bearing on either the RfD or the decision not to ask for a developmental neurotoxicity study.

Rationale

In the 90 day study (MRID No. 431512-02), forelimb grip strength was significantly decreased in females (18-25%) between weeks 5-14 and decreased roughly 20% in high dose males at week 14.

The DER cites only the effect in females and cites a number of reasons why this effect to support its conclusions that "it is unlikely that these decreases in mean forelimb grip strength values for high dose females constitute a neurotoxicological effect." These reasons are:

- no effects in males;
- no effects in hind limb grip strength;
- no effects in other FOB parameters;
- no effects in motor activity;
- and no effects in neuropathology.

First, I think there is an effect in high dose males at week 14 of around 20% with respect to controls and a decrease of 10% with respect to week 9 in the same animals. Between week 9 and 14,

both males at the mid and high dose show a decline in this measure, while low dose and control animals show an increase.

Second, in the acute study (MRID No. 431323-01), at 300 mg/kg where many toxic effects were noted, both sexes also showed a significant decrease in this measure.

While there are no effects in hind limb grip strength, why would one be expected? If both fore and hind limb grip strength were impaired, a generalized weakness would be a more cogent hypothesis. The specificity of this effect, then, should not be viewed as somehow reducing the importance or likelihood of its mechanism.

There is no clear relation between this measure and motor activity.

On the other hand, one might expect some measures in the FOB might be affected, such as the approach responses, or that neuro-pathological changes might have been affected. However, there are many dysfunctions caused by neurotoxicants that have no ready pathological correlates, and the quantitative measures like grip strength in general provide a better chance than less well quantified FOB measures of showing any effect. In summary, while the evidence is somewhat limited, it does appear to be an effect of treatment and is seen in both sexes after both acute or 90 days of exposure at high doses.

It is my position then: 1) that these are adverse effects relevant for setting NOELs and LOELs (with which there is general agreement); and 2) that a neurotoxic mechanism can neither be confirmed nor ruled out.