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MEMORANDUM

SUBJECT: *SULFOSATE* - **Second Report** of the Hazard Identification Assessment Review Committee.

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and
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THROUGH: K. Clark Swentzel, Chairman,
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Health Effects Division (7509C)
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TO: Melba Morrow, Branch Senior Scientist
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PC Code: 128501

On June 12, 1998 the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to reexamine the neurotoxicity hazard assessment/characterization for **Sulfosate**. This was a follow-up meeting to the HIARC meeting held on April 26, 1998 to re-assess the Reference Dose (RfD) established in 1994 as well as the toxicological endpoints selected for acute dietary and occupational/residential exposure risk assessments for **Sulfosate**. The HIARC addressed the potential enhanced sensitivity of infants and children from exposure to sulfosate as required by the Food Quality Protection Act (FQPA) of 1996 at both meetings. This report includes the Committee's conclusions from both meetings.

Committee Members in Attendance

Members present were: Karl Baetcke, Bill Burnam, Robert Fricke. Sue Makris, Melba Morrow, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman). Member(s) in absentia: Karen Hammernik, Mike Metzger and John Redden. Data were presented by Marion Copley of the Registration Action Branch 1 and Kathleen Raffaele of the Toxicology Branch 2.

Data Presentation: _____
and
Report Preparation Marion Copley, D.V.M., D.A.B.T.

Report Concurrence: _____
Jess Rowland
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I. INTRODUCTION

On April 26, 1998 the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-assessed the Reference Dose established in 1994, selected the toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments, and addressed the potential enhanced sensitivity of infants and children from exposure to sulfosate as required by the Food Quality Protection Act (FQPA) of 1996.

In a follow-up meeting held on June 12, 1998 the HIARC reexamined the neurotoxicity studies for better characterization of the neurotoxic potential of **Sulfosate**. This report includes information from both meetings.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (RfD)

Study Selected: Acute Rat Neurotoxicity

Guideline #: 81-8

MRID No.: 43132301

Executive Summary: In an acute neurotoxicity study, Glyphosate Trimesium Technical (purity 59.4%, Lot No. F47 D7534/36) was used to treat Alpk:APfsD rats, 10/sex/dose by gavage at 1 ml/100 g bw with doses of 0, 30, 100 or 300 mg/kg. Adequate positive control data was provided. At **300 mg/kg** there was death, ptosis, decreased activity, decreased splay reflex, upward curvature of spine, chromodacryorrhea, staining around the nose, decreased bodyweight and food consumption (males), shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, increased time to tail flick, decreased landing foot splay, decreased forelimb grip strength, decreased hindlimb grip strength, decreased motor activity. There was no microscopic evidence of neurotoxicity. There were no indications of neurotoxicity below a lethal dose. **The LEL was 300 mg/kg based on mortality, neurologic signs described above and decreased body weight and food consumption. The NOEL was 100 mg/kg.**

Dose and Endpoint for Risk Assessment: NOEL = 100 mg/kg based on mortality, decreased body weight and food consumption, and neurotoxicity at 300 mg/kg (LOEL).

Uncertainty Factor: 100 (10 x for inter-species extrapolation and 10 x for intra-species variations)

$$\text{Acute RfD} = \frac{100 \text{ mg/kg}}{100 \text{ (UF)}} = 1.0 \text{ mg/kg}$$

Comments about Study and Endpoint: This endpoint is appropriate for this risk assessment, since it was observed after a single dose in the acute neurotoxicity study.

This risk assessment is required.

B. CHRONIC DIETARY [Reference Dose (RfD)]

Study Selected: One-Year Chronic Dog Study

Guideline #: 83-1b

MRID Nos.: 40214005 and 41235902

Executive Summary: In a chronic oral gavage study, beagle dogs (5/sex/dose) were treated with sulfosate (SC-0224 (batch # EHC 0469-15;WRC# 8108-24-1; 56.2% pure)) for 1 year at doses of 0, 2,10, or 50 mg/kg/day. Signs of toxicity were limited to the 50 mg/kg/day group females and included transient salivation (1/5 at 10 mg/kg/day and 5/5 at 50 mg/kg/day) and emesis (single episodes in 3/5 dogs). The decreased LDH in females (53, 41, 32, 15*, from control to high dose) at 12 months is of questionable biological significance. The high dose was however, supported by subchronic studies where transient salivation and emesis again occurred at 50 mg/kg/day in a 90 day study and at 75 mg/kg/day in a 28 day study; with death occurring within 3 days at 150 mg/kg/day in the 28 day study. **The LOEL is 50 mg/kg/day based on salivation and emesis and support from shorter term studies also with emesis and salivation. The NOEL is 10 mg/kg/day.**

Dose and Endpoint for Risk Assessment: NOEL =10 mg/kg/day based on salivation and emesis at 50 mg/kg/day (LOEL).

Uncertainty Factor: 100 (10 x for inter-species extrapolation and 10 x for intra- species variation).

$$\text{Chronic RfD} = \frac{10 \text{ mg/kg/day}}{100(\text{UF})} = 0.10 \text{ mg/kg/day}$$

Comments about Study and Endpoint: The HIARC concurs with the RfD established in 1994.

This risk assessment is required.

C. Occupational/Residential Exposure

1. Dermal Absorption: There are no dermal absorption studies available for review.

Dermal Absorption Factor: Dermal absorption factor is not applicable since no toxicological endpoints were identified for dermal risk assessments.

2. Short-Term Dermal - (1-7 days)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint: Not Applicable

Comments about Study/Endpoint: The database included a 21-day dermal toxicity study with the technical product and another 21-day dermal toxicity study with the formulation product. In the study with the technical product, for systemic toxicity, the NOEL was 1000 mg/kg/day (Limit-Dose), the highest dose tested; a LOEL was not established. In the study with the formulation product, the NOEL was 250 mg/kg/day and the LOEL was 1000 mg/kg/day based on minimal sciatic nerve fiber degeneration of unstated severity. The Committee determined that the potential for risk via the dermal route is minimal based on: 1) the low dermal/systemic toxicity demonstrated in the 21-dermal toxicity studies (discussed below); 2) the current use patterns (agricultural) do not indicate an exposure concern; and 3) there are no registered residential uses at the present time. **At this time dermal risk assessments are not required. However, if residential uses, are requested or there is a residential post application exposure, the issue of dermal risk assessment will need to be reexamined.**

No systemic toxicity was seen following 15 repeated dermal application of the technical material [57.3%] at doses of 0, 10, 100, and 1000 mg/kg/day, 6 hours /day, 5 days/week over a 3 week period to male and female rabbits. For systemic toxicity, the NOEL was 1000 mg/kg/day (Limit Dose). There was mild erythema at the application sites in all of the treatment groups (MRID No.4089702).

In another 21-day dermal toxicity study, male and female Wistar rats received repeated dermal applications of the formulation product Touchdown [4 LCE formulation, 39.8%] at 0, 25, 250, or 1000 mg/kg/day for 6 hours/day, for 21 days. At 25 and 1000 mg/kg/day, but not at 250 mg/kg/day, there was slight increases in testes weight with no microscopic changes. There were no effects at 250 mg/kg/day. At 1000 mg/kg/day, there were skin irritation effects and occasional sciatic nerve fiber degeneration of unstated severity [1/5 males and 2/5 females]. These effects were not observed in controls. For systemic toxicity, the NOEL was 250 mg/kg/day and the LOEL was 1000 mg/kg/day based on sciatic nerve findings at 1000 mg/kg/day (MRID No.41209904).

This risk assessment is **NOT** required at this time.

2. Intermediate-term Dermal (1-Week to Several Months)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not Applicable

Comments about Study and Endpoint: **At this time dermal risk assessments are not required. However, if residential uses, are requested or there is a residential post application exposure, the issue of dermal risk assessment will need to be reexamined** (See Short-Term Dermal for details).

This risk assessment is **NOT** required at this time.

3. Long-term Dermal (Several Months to Lifetime)

Study Selected: None

MRID No.: None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study and Endpoint: **At this time dermal risk assessments are not required. However, if residential uses, are requested or there is a residential post application exposure, the issue of dermal risk assessment will need to be reexamined.** (See Short-Term Dermal for details).

This risk assessment is **NOT** required at this time.

4. Inhalation Exposure (All Time periods).

Except for an acute inhalation toxicity study no other inhalation studies are available in the toxicology data base.

Based on the high inhalation exposure potential for proposed use patterns, HIARC selected oral NOELs for inhalation risk assessments. Since an oral dose is used, risk assessments should follow the route-to-route extrapolation as below:

Step 1 The inhalation exposure component (i.e. ug a.i/L./day) using 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** [mg/kg/day].

Step II The converted dose should then be compared to the oral NOELs to calculate the MOEs. The NOELs are as follows:

For Short-Term:	NOEL = 100 mg/kg/day
For Intermediate-term:	NOEL = 10 mg/kg/day
For Chronic Exposures	NOEL = 10 mg/kg/day

These NOELs were also used for establishing the acute and chronic RfDs.

This risk assessment is required.

D. Margins of Exposure for Occupational/Residential Exposures

Margins of exposure (MOEs) are not required for occupational/residential exposure risk assessments since toxicological endpoints were not selected for these exposure scenarios. A MOE of 100 is acceptable for inhalation risk assessments (any time period). If the use pattern changes and a dermal risk assessment is required, a MOE of 100 is adequate (any time period).

E. Recommendation for Aggregate Exposure Risk Assessments

Not required; there are no registered residential uses at the present time.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 40214007, 41209905, 41209907

Discussion of Tumor Data: No evidence of carcinogenicity.

Adequacy of the Dose Levels Tested: Doses tested were 0, 0, 100, 500, or 1000 ppm for 24 months in Sprague-Dawley rats. Palatability problems were observed in that food consumption and body weight were both decreased at 1000 ppm. Results from subchronic studies indicate that at least ½ MTD was used in the 2-year rat study. It was believed that the chemical was adequately tested for carcinogenicity.

2. Carcinogenicity Study in Mice

MRID No. 40214006, 41209907

Discussion of Tumor Data No evidence of carcinogenicity.

Adequacy of the Dose Levels Tested Doses were 0, 100, 1000, or 8,000 ppm in CD-1 mice. Decreased body weight and food consumption occurred at 8,000 ppm, and duodenal hyperplasia in females at 8,000 ppm.

3. Classification of Carcinogenic Potential: The HED/RfD Committee (document dated 26-JUL-1994) has classified sulfosate as a "Group E" - no evidence of carcinogenicity in male and female rats as well as in male and female mice. The current HIARC Committee saw no reason to modify this decision.

IV. FQPA CONSIDERATIONS

1. Adequacy of the Database:

Acceptable hen delayed neurotoxicity, acute and subchronic rat neurotoxicity screening studies have been submitted to the Agency. Acceptable prenatal toxicity studies in rats and rabbits and a 2-generation reproductive toxicity study in rats on sulfosate have been submitted to the Agency. However, a developmental neurotoxicity is required based on the neurotoxicity observed in dogs, rats and mice (see below).

2. Neurotoxicity Data:

Sulfosate has evidence of neurotoxicity in several studies in rats, dogs and the mice.

The following three executive summaries present the relevant findings from acceptable hen and rat (acute and subchronic) neurotoxicity studies. Following that, are brief summaries of other sulfosate studies with signs of neurotoxicity. Following these summaries is the characterization of the neurotoxicity issues raised by the data base.

81-7 Hen delayed neurotoxicity study - In an acute neurotoxicity study (MRID 43151201), white leghorn chickens (6 hens/group in control groups, 8 hens/group in treated groups) were treated with Tech ICIA-0224 (purity: 56.9%, Lot No.4921-50-2; 8289-35-1) by gavage at doses of 0, 500 or 5000 mg/kg in 5 ml/kg water. TOCP (500 mg/kg) was the positive control. Each animal was dosed twice during the study; day 1 and day 22. Each animal was evaluated up to day 41 (or 42). At 500 mg/kg there was diarrhea starting a few days after each dosing, lasting for 2-3 days. At 5000 mg/kg there was diarrhea, changes in comb appearance, early decreased food consumption and decrease in egg production. No

indications of delayed neurotoxicity were observed. The positive control indicated the appropriate clinical signs of toxicity, increased ataxia and microscopic observations for an organophosphate. **The NOEL for systemic toxicity was 500 mg/kg. The LEL for systemic toxicity was 5000 mg/kg.**

81-8 Acute Neurotoxicity Study - In an acute neurotoxicity study (MRID 43132301), Glyphosate Trimesium Technical (purity 59.4%) was used to treat Alpk:APfsD rats, 10/sex/dose by gavage at 1 ml/100 g bw with doses of 0, 30, 100 or 300 mg/kg. Adequate positive control data was provided. At 300 mg/kg there was death, ptosis, decreased activity, decreased splay reflex, upward curvature of spine, chromodacryorrhea, staining around the nose, decreased bodyweight and food consumption (males), shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, increased time to tail flick, decreased landing foot splay, decreased forelimb grip strength, decreased hindlimb grip strength, decreased motor activity. There was no microscopic evidence of neurotoxicity. There were no indications of neurotoxicity below a lethal dose.. **The LEL was 300 mg/kg based on mortality, neurologic signs described above and decreased body weight and food consumption. The NOEL was 100 mg/kg.**

82-7 Subchronic Neurotoxicity Screening Battery - Technical glyphosate trimesium (sulfosate, 59.4%, Batch Lot No. F47 D7534/36; CTL Y06380/036) was tested in a 90 day neurotoxicity feeding study (MRID 43151202) in Alpk:APfsD rats. Rats (12/sex/group) received either 0, 200, 600, or 2000 ppm (0, 15.6, 47.6 or 153.2 mg/kg/day for males; 0, 18.2, 54.4 or 171.0 mg/kg/day for females) in diet. Six/sex/dose group received complete necropsy and neurohistopathology. Positive control data were provided.. Clinical signs of toxicity, body weights, food consumption, functional battery, motor activity and neuropathology parameters were measured and recorded regularly. Positive control data were provided. At **2000 ppm**, decreased body weights (16% for males and 9% for females), food consumption and utilization were observed. In addition, mean forelimb grip strength values for high dose females were statistically significantly decreased over the control values during weeks 5-14 (75 - 82% of controls). There was no microscopic evidence of neurotoxicity. The significance of the decreased grip strength as a neurotoxicological effect is less certain since there were no effects in mean hindlimb grip strength for high dose females, in either of the mean grip strength values at any time period for males, in any of the other functional battery parameters, in motor activity values or in neuropathology microscopic examinations for either sex. However, it did occur at all time points, was statistically significant, and signs of neurotoxicity occur in other studies **The LEL is 2000 ppm (153.2 mg/kg/day) based on decreases in mean body weight, food consumption, food utilization and mean forelimb grip strength values. The NOEL is 600 ppm (47.6 mg/kg/day).**

The following neurotoxic effects were seen following exposure to sulfosate for varying durations in several species.

A. Dogs

1. In a 28-day gavage study (summary only available), clinical signs (decreased activity, emesis, salivation, tremors and/or shaking) were seen at 36 mg/kg/day, with the NOEL at 20 mg/kg/day. Details of incidence (number of animals or persistence) and severity of effects was not included in the summary.
2. In a 90-day gavage study (MRID 41209903, 4163301), salivation and emesis were seen in both sexes in a dose-related manner (incidence for emesis was 1, 2, 3, 6 for males, 4, 0, 3, 6 for females at 0, 2, 10, and 50 mg/kg/day, respectively; incidence for salivation (transient) was 0, 0, 1, 3 for males, 0, 0, 0, 5 for females). First day of observation was earlier for high dose groups, but the number of observed incidences was not included in the DER. In addition, dilated lateral ventricles (brain) were observed in 2 high dose females macroscopically, and hydrocephalus was observed in one high dose female microscopically. [n=6/sex/group]
3. In a 90-day capsule study (MRID 44246704 - preliminary review), increased incidence of salivation at dosing was seen in two high dose males (total of 92 observations from weeks 2-14 compared to 3 observations in 1 animal from weeks 10-13 in control group); in addition, salivation was observed 15 times in 2 high dose males unrelated to dosing, with no observations in any other group. Increased incidence of salivation at dosing was also seen in high dose females (105 observations in 3 animals from weeks 4-14, no observations in any other group); salivation unrelated to dosing was also increased (32 observations in 2 animals from weeks 3-13). One high dose female was sacrificed in extremis on day 2 (the animal was found cold, recumbent, and comatose), and the dose was reduced in one high dose female who displayed multiple symptoms (tremors, recumbency, paddling of limbs) at two or three separate time points during the study (weeks 5, 7, and 11). On these occasions, the occurrence of symptoms was preceded by increased severity of salivation; dosing was stopped at the appearance of symptoms. When symptoms resolved, dosing was resumed, but symptoms recurred. After the second appearance of symptoms and dosing discontinuation, dosing was resumed at a lower level (40 mg/kg/day); severe symptoms did not recur at that dose level, but did recur when dosing was briefly returned to the 50 mg/kg/day level. Dosing was then resumed at 40 mg/kg/day to study termination. Upon pathological evaluation, hydrocephalus was found in one high dose male, a different high dose male had unilateral cataract, and GI muscle hypertrophy was seen in a third high dose male. [Doses were 0, 10, 25, or 50 mg/kg/day; n=4/sex/group].
4. In a one year gavage study (MRID 40214005), 'transient salivation' was observed in one mid-dose female and 5 high dose females (no specific incidence information was provided in the DER). On histopathological evaluation, hydrocephalus was found in one high dose male and one mid-dose female. [Doses were 0, 2, 10, and 50 mg/kg/day, n=5/sex/group].

B. Mice

1. In a 2-year oncogenicity study in mice (MRID 40214006), there was increased incidence of lumbar spinal white matter degeneration in males only, as follows (incidence given as percent): 2, 2, 4, 4, 8% for 2 control groups, 100, 1000, 8000 ppm groups respectively. The increased incidence of white matter degeneration was statistically significant, and was used to set the LOEL for males for the study at the high dose, with the NOEL at 1000 ppm.

C. Rats

1. Developmental toxicity (MRID 00126618, 00132183, 00155387): The maternal NOEL was 100 mg/kg/day, based on decreased body weight gain, decreased food intake, and clinical signs (salivation [7/20], lethargy [8/20], and chromorrhinorrhea [9/20]) at 333 mg/kg/day. Incidences of clinical signs in controls were 0/24 for salivation, 0/24 for lethargy, and 2/24 for chromorrhinorrhea. [Doses were 0, 30, 100, 333 mg/kg days 6-20 of gestation, by gavage].

2. 21-day dermal toxicity (MRID 41209904): In a 21-day dermal toxicity study, sciatic nerve degeneration was seen in 1/5 high dose males and 2/5 high dose females. [Doses were 0, 25, 250, and 1000 mg/kg, 6 hrs./day for 21 days, n=5/sex/group, histopathology was conducted on control and high dose groups only].

D. Neurotoxicity Characterization

Sulfosate is a neurotoxic chemical, which produces clinical findings such as **salivation**, tremors, emesis, decreased activity in dogs and/or rats. Salivation was the most consistent sign, and in dogs may have served as a precursor to more severe symptoms. In one study, salivation stopped upon withdrawal of sulfosate and recurred upon reintroduction of treatment.. Dogs appear to be the most sensitive species for these effects, with high intra-individual variability in sensitivity. Acute neurotoxicity effects observed after a single dose of 300 mg/kg in the rat included ptosis, decreased activity, decreased splay reflex, upward curvature of spine, shaking, sides pinched in, signs of urinary incontinence, irregular breathing, hunched posture, abnormal or staggering gait, increased time to tail flick, decreased landing foot splay, decreased forelimb grip strength, decreased hindlimb grip strength, decreased motor activity. There was also death at this dose. In the subchronic rat neurotoxicity study, the decreased forelimb grip strength observed at 153 mg/kg/day, in females only, may also have been due to treatment. **Hydrocephalus** or dilated ventricles were observed in at least one animal at the HDT (50 mg/kg/day) in adult dogs in all the dog studies, following both 90-days (gavage or capsule) and one year of dosing. This finding was never seen in controls or low dose groups. Hydrocephaly and/or dilated ventricles in dogs of this age may have been due to inherent asymptomatic incidences in the beagle (Vullo et al.,

1997), but it was noted that these animals were not supplied by the same breeding colony, and the incidences were only observed at the high dose levels across several studies.

Therefore, it was agreed by the Committee that these findings could not be dismissed.

Neuropathology was observed in the 21-day rat dermal study (sciatic nerve degeneration) at 1000 mg/kg, and the 2-year chronic mouse study (degeneration of the sciatic nerve, lumbar spinal root, and lumbar spinal white matter in males) at 991 mg/kg. Although these findings were previously discounted due to lack of supporting neuropathology data in the acute and subchronic neurotoxicity studies in rats, the overall neurotoxicity profile of the chemical indicated that the neuropathology could be a treatment-related effect of concern.

3. Developmental Toxicity Data

83-3a Prenatal Developmental Study - Rat - In a developmental toxicity study (MRID 00132183), rats (25/dose) were treated with sulfosate (SC-0224 19.2% ai; Lot No. EHC-0355-25), by gavage on gestation days 6 through 20 at dose levels of 0, 30, 100, or 333 mg/kg/day. The test material was dissolved in water and administered in a volume of 5 ml/kg. Treatment related effects were limited to the high dose dams and included decreased body weight (17 % less than the control), body weight gain and feed consumption. There was also salivation, chromorrhinorrhea and lethargy after dosing in this group ($p < 0.05$). **The Maternal LOEL is 333 mg/kg/day based on decreased body weight, feed consumption and body weight gain along with increased incidences of salivation, chromorrhinorrhea, and lethargy after dosing. The Maternal NOEL is 100 mg/kg/day.** Developmental signs of toxicity were limited to the high dose and included decreased fetal body weight (5.0, 4.9, 4.9, 4.2* gm, controls to high dose). **The Developmental toxicity LOEL is 333 mg/kg/day based on decreased fetal body weight. The Developmental toxicity NOEL is 100 mg/kg/day.**

83-3b Prenatal Developmental Study - Rabbit - In a developmental toxicity study (MRID 00155526), New Zealand white rabbits (15/group except 21 at the high dose) were treated by gavage with sulfosate (SC-0224, purity: 56.2%, Lot No. EHC-0355-25) from gestation days 7 - 19. The test material was dissolved in water and administered in a volume of 2 ml/kg at dose levels of 0, 10, 40 or 100 mg/kg/day. **The Maternal LOEL is 100 mg/kg/day (6 deaths in 17 pregnant doses, 4 abortions in the 11 survivors along with decreased body weight, feed consumption and body weight gain). The Maternal NOEL is 40 mg/kg/day.**

The developmental LOEL is 100 mg/kg/day based on decreased number of live fetuses/doe for 7 surviving rabbits (5.4 versus 7.4 in controls), 4 rabbits aborted their litters. Having only 7 litters does not give a sufficiently higher number of animals to absolutely conclude that no developmental toxicity is occurring, particularly in light of the massive losses to death and abortions. The developmental NOEL is 40 mg/kg/day.

4. Reproductive Toxicity:

83-4 Two-Generation Reproduction Study - Rat - In a 2-generation reproduction study (MRID 00154273), 20 male and 30 female/group Sprague-Dawley rats received sulfosate (SC-0224 tech. Purity: 19.2% a.i.) at dose levels of 0, 150, 800, or 2000 ppm in the diet (average for P0 and P1 - males - 0, 6.0, 35, 88.5 mg/kg/day; females - 0, 8, 41, 98 mg/kg/day). **The systemic LEL is 800 ppm (35 and 41 for males and females) based on a decrease in absolute and sometimes relative organ weights in both generations (thymus, heart, kidney and liver) at 800 and 2000 ppm and a decrease in body weights and body weight gains during the pre-mating period at 2000 ppm. The Systemic NOEL: 150 ppm (6 and 8 for males and females).**

The reproductive/developmental LOEL is 800 ppm (35 and 41 for males and females) is based on decreased litter size in F0a and F1b litters at 2000 ppm and on decrease in mean pup weights during lactation in second litters at 800 ppm & in all litters at 2000 ppm. The reproductive/developmental NOEL is 150 ppm (6 and 8 for males and females).

5. Determination of Susceptibility

The data provided no indication of increased susceptibility in rats or rabbits from in utero and/or post natal exposure to sulfosate. In the prenatal developmental toxicity study in rats, evidence of developmental toxicity was seen only in the presence of maternal toxicity. In the developmental toxicity study in rabbits, developmental toxicity was seen in the presence of maternal toxicity at the highest dose level. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which results in evidence of parental toxicity. It should be noted that a developmental neurotoxicity study is required.

6. Recommendation for a Developmental Neurotoxicity Study

The following is a result of the HIARC reevaluation of the neurotoxicity hazard assessment and need for a developmental neurotoxicity study the meeting dated 12-JUN-1998.

The following information was considered in support of need for a developmental neurotoxicity study for sulfosate. Based upon a weight of evidence consideration of all these factors, the Committee decided **to require the conduct of a developmental neurotoxicity study with sulfosate** to evaluate the potential for effects on functional development

a) Evidence that support requiring a developmental neurotoxicity study:

- » Sulfosate is a neurotoxic chemical (details are described in the summary document), which produces clinical findings such as salivation, tremors, emesis, decreased activity in dogs and/or rats. Acute neurotoxic effects were observed after a single dose of 300

mg/kg in the rat.

- » Hydrocephalus or dilated ventricles were observed at the HDT (50 mg/kg/day) in adult dogs following 90-days (gavage or capsule) or 1-year of dosing. Hydrocephaly and/or dilated ventricles in dogs of this age may have been due to inherent asymptomatic incidences in the beagle (Vullo et al., 1997), but it was noted that these animals were not supplied by the same breeding colony, and the incidences were only observed at the high dose levels across several studies. Therefore, it was agreed by the Committee that these findings could not be dismissed.
- » Neuropathology was observed in the 21-day rat dermal study (sciatic nerve degeneration) at 1000 mg/kg, and the 2-year chronic mouse study (degeneration of the sciatic nerve, lumbar spinal root, and lumbar spinal white matter in males) at 991 mg/kg. Although these findings were previously discounted due to lack of supporting neuropathology data in the acute and subchronic neurotoxicity studies in rats, the overall neurotoxicity profile of the chemical indicated that the neuropathology could be a treatment-related effect of concern.

b) Evidence that do not support asking for a developmental neurotoxicity study:

- » No evidence of treatment-related anomalies in the development of the fetal nervous system were observed in the prenatal developmental toxicity studies in either rats or rabbits, at maternally toxic oral doses up to 333 or 100 mg/kg/day, respectively. In the rat study, anomalies of the brain were observed in all groups, including control, at similar incidences (dilation of the 4th ventricle), or only in low- or mid-dose. In the rabbit study, dilation of the 4th ventricle was seen at all dose levels except for the HDT and at a higher incidence in controls; hydrocephalus was observed at a non-treatment-related distribution (1/1/0/2 fetuses).
- » No clinical observations indicative of neurobehavioral or functional abnormalities were reported for pups or second generation (F1) adults in the two-generation reproduction study in rats.
- » No effects on brain weight were observed in any of the guideline studies in which these parameters were measured.
- » No evidence of cholinesterase inhibition was observed for sulfosate.
- » Sulfosate is not a potent toxicant; it has an oral LD₅₀ of 750 mg/kg in rats.
- » SAR: glyphosate, a related chemical, is not neurotoxic

7. Determination of the FQPA Safety Factor:

The determination of the FQPA safety factor is referred to the FQPA Safety Factor Committee. The weight of the evidence should take into account the lack of evidence of susceptibility in acceptable studies as well as the requirement for a developmental neurotoxicity study.

8. Additional information from the literature (IF AVAILABLE) None

V. DATA GAPS

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158, however a developmental neurotoxicity study in the rat is required.

VI. HAZARD CHARACTERIZATION

Sulfosate is a herbicide, which consists of trimethylsulfonium glyphosate. The cationic component is trimesium and the anionic component is glyphosate. The toxicology data base provides no evidence that sulfosate has anticholinesterase activity, as evidenced by decreased cholinesterase activity in rats and dogs following subchronic and chronic exposures.

In acute toxicity studies, sulfosate exhibits low to high toxicity, depending on the route of exposure and the species used. Sulfosate is not toxic at low dose oral levels and *via* the inhalation route in rats. In rabbits, sulfosate is not acutely toxic *via* the dermal route, is non-irritating to the skin, but is a severe eye irritant. It produces a weak dermal sensitization reaction in guinea pigs.

In addition, sulfosate is unpalatable in the rodent diet, since in both subchronic and chronic studies in rats and mice, decreased weight gain could be correlated with decreased food consumption with little change in feed efficiency.

There is no indication of an increased susceptibility of fetuses or offspring in rats or rabbits after prenatal and/or postnatal exposure to sulfosate. A similar finding was made with respect to glyphosate, a structurally related pesticide.

There are no data gaps for the assessment of effects of sulfosate following *in utero* exposure or the effects on young animals following early exposure (exception - developmental neurotoxicity).

Sulfosate is classified as a Group E carcinogen, based on the absence of tumorigenicity in

two species of animals in two acceptable studies.

The main difference between sulfosate and glyphosate can best be seen in a comparison of their RfDs. The RfD for glyphosate is 2.0 mg/kg/day and the RfD for sulfosate is 0.10 mg/kg/day [a 20 fold difference]. The enhanced toxicity of sulfosate in comparison to glyphosate is due to the presence of the trimesium cation in the sulfosate molecule.

There are no data gaps for the standard Subdivision F Guideline requirements for a food-use chemical by 40 CFR Part 158, however a developmental neurotoxicity study in the rat is required. This is based on the weight -of-the-evidence for concerns of neurotoxicity in the mouse oncogenicity study, the gavage dog studies, 21-day dermal toxicity study in rats, and acute and subchronic neurotoxicity studies in the rat. Signs of neurotoxicity due to sulfosate included FOB effects in the rat neurotoxicity studies, treatment related salivation and emesis in the dog. There were also concerns for hydrocephalus in all dog studies (at least one dog/study at the high dose, none in controls) and possible treatment related histopathology in the mouse carcinogenicity and 21 day dermal rat studies.

VII. ACUTE TOXICITY

Acute Toxicity of SULPHOSATE

Guideline No.	Study Type	MRID #(S)	Results	Toxicity Category
81-1	Acute Oral	00126608, 00132172	LD50 = 748 mg/kg	III
81-2	Acute Dermal	00126608, 00132173	LD50 = 2000 mg/kg	III
81-3	Acute Inhalation	00126609	LC50 = 6.9 m/L	IV
81-4	Primary Eye Irritation	00126608, 00132172	Slight Irritation	III
81-5	Primary Skin Irritation	00126608, 00132172	0.19/4.00	III
81-6	Dermal Sensitization	00154270	slight sensitizer	

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOEL= 100	Clinical signs indicative of neurotoxicity including tail flick, landing foot splay, forelimb grip strength, hindlimb grip strength and motor activity.	Acute Neurotoxicity-Rat
	UF = 100		
	Acute RfD = 1.0 mg/kg		
Chronic Dietary	NOEL = 10	Clinical signs indicative of neurotoxicity (emesis and salivation).	Chronic Toxicity - Dog
	UF = 100		
	Chronic RfD = 0.10 mg/kg/day		
Short-, Intermediate or Long-Term (Dermal)	None	Based on the lack of systemic toxicity at 1000 mg/kg/day (NOEL) with the technical product and minimal sciatic nerve fiber degeneration of unstated severity at 1000 mg/kg/day (LOEL) (NOEL = 250 mg/kg/day) with the formulation in the 21-day dermal toxicity studies, the Committee determined that the potential for risk via the dermal route is low due to low toxicity and at this time the current use patterns (agricultural) do not indicate an exposure concern. At this time dermal risk assessments are not required.	
Short Term (Inhalation) ^a	Oral NOEL= 100	Clinical signs indicative of neurotoxicity including tail flick, landing foot splay, forelimb grip strength, hindlimb grip strength and motor activity.	Acute Neurotoxicity-Rat
	MOE = 100		
Intermediate & Long-Term (Inhalation) ^a	Oral NOEL= 10	Clinical signs indicative of neurotoxicity (emesis and salivation).	Chronic Toxicity - Dog
	MOE = 100		

a= Since an oral NOEL was selected, an inhalation absorption factor (100%) should be used.

Reference: Vullo, T., E. Korenman, R.P. Mazo, D.G. Gonez, M.D. Deck, and P.T. Cahill. 1997. Diagnosis of cerebral ventriculomegaly in normal adult beagles using quantitative MRI. *Vet. Radiol. Ultrasound*, Jul.-Aug. 38 (4):277-81.