Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Proposed Regulatory Decision Document PRDD2005-04

EXIT™ ISP

The reduced-risk integrated systems product EXIT™ ISP and associated end-use product EXIT™ Concentrate Rodenticide for the control of Richardson's Ground Squirrels are proposed for registration under of the Pest Control Products Regulations.

This Proposed Regulatory Decision Document provides a summary of data reviewed and the rationale for the proposed full registration of these products. The Pest Management Regulatory Agency (PMRA) will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications at the address listed below.

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has reviewed the submission for full registration of EXIT™ Integrated Systems Product (also referred to as EXIT™ ISP) containing sodium α-olefin sulfonate (AOS) and mustard seed powder (MSP) and the associated end-use product EXIT™ Concentrate Rodenticide, manufactured by Exit Holdings, for the control of Richardson's Ground Squirrels.

The PMRA and the United States Environmental Protection Agency (USEPA) jointly reviewed these products as reduced-risk products (Group 1A Reduced Risk Joint Reviews) within the North American Free Trade Agreement's Technical Working Group on Pesticides Joint Review Program.

The PMRA had previously issued a temporary registration (Regulatory Note REG2003-04) for these products with the requirement that data be provided pertaining to the intermediate products formed during the biotransformation of AOS in soil, with reference to laboratory studies or to the scientific literature. This was addressed satisfactorily, and this document details the scientific rationale used to support the registration of these products.

The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of EXIT™ ISP and the associated end-use product EXIT™ Concentrate Rodenticide. The Agency has concluded that the use of EXIT™ ISP and the end-use product EXIT™ Concentrate Rodenticide in accordance with the label has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm. Based on the considerations outlined above, the use of EXIT™ ISP and the end-use product EXIT™ Concentrate Rodenticide for the control of Richardson's Ground Squirrels in rangeland, ornamental plantings, orchards, golf courses, parks, nurseries and non-crop rights of way in southern Alberta, Saskatchewan and southwestern Manitoba is proposed for full registration, pursuant to the Pest Control Products Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

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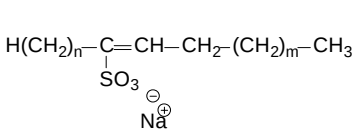
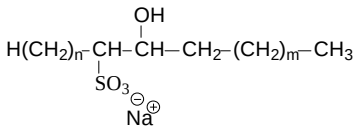
1.0 The Active Substance, its Properties and Uses

1.1 Identity of the Active Substances and Preparation Containing Them

There are two active components in EXIT™ ISP: sodium α-olefin sulfonate (AOS) and mustard seed powder (MSP). Mustard seed powder is a natural product derived from the white mustard seed plant *Brassica hirta*. It is a complex mixture of substances (not a distinct chemical entity). For this reason, there is no chemical name from the International Union of Pure and Applied Chemistry (IUPAC) or the Chemical Abstracts Service (CAS), CAS chemical name, CAS number, molecular formula, molecular weight or structural formula available for MSP. Details on the identification of AOS and MSP are provided below.

Identification of the Technical Grade Active Ingredient

Active substance		Mustard seed powder and α-olefin sulfonate, sodium
Function		Rodenticide
Chemical name		
1.	International Union of Pure and Applied Chemistry (IUPAC)	Sodium α-olefin sulfonate
2.	Chemical Abstracts Service (CAS)	Alkyl (C14-C16) olefin sulfonate, sodium salt
CAS number		Mustard seed powder has no CAS number Sodium α-olefin sulfonate: 68439-57-6
Molecular formula		$C_{14\text{-}16}H_{27\text{-}31}SO_3Na$
Molecular weight		298.4–326.5
Structural formula		 n = 0–12 n + m = 10–12 Position of unsaturation varies
		 n = 0–12 n + m = 10–12 Position of hydroxyl group varies

Nominal purity of active	Mustard seed powder (*Brassica hirta*) 10.89% (limits 10.35–11.43%) Sodium α-olefin sulfonate 6.91% (limits 6.56–7.26%)
Identity of relevant impurities of toxicological, environmental or other significance	Technical grade mustard seed powder with α-olefin sulfonate does not contain any impurities or microcontaminants known to be Toxic Substances Management Policy (TSMP) Track 1 substances

1.2 Physical and Chemical Properties

The physicochemical properties of the technical grade active ingredients, AOS and MSP, are provided in Table 1.2.1. The physicochemical properties of the end-use product, EXIT™ Concentrate Rodenticide, are provided in Table 1.2.2.

Table 1.2.1 Technical Product: EXIT™ ISP

Property	Result	Comment
Colour and physical state	Yellow liquid suspension	
Odour	Mild	
Melting point or range	Waiver accepted	
Boiling point or range	Waiver accepted	
Density	1.034	
Vapour pressure at 20°C	Waiver accepted	
Henry's law constant	Waiver accepted	
Ultraviolet (UV)–visible spectrum	For sodium α-olefin sulfonate λ_{max} at 260–270 nm	AOS has a low potential for UV-induced phototransformation under normal environmental conditions.
Solubility in water at 20°C	Mustard seed powder is insoluble in water and sodium α-olefin sulfonate is highly soluble.	

Property	Result	Comment
Solubility in organic solvents	Waiver accepted	
n-Octanol–water partition coefficient (K_{ow})	Waiver accepted	
Dissociation constant (pK_a)	Waiver accepted	
Stability (temperature, metal)	Stable under normal, ambient conditions.	

Table 1.2.2 End-use Product: EXIT™ Concentrate Rodenticide

Property	Result
Colour	Light amber
Odour	Strong shoe polish odour
Physical state	Liquid suspension
Formulation type	Emulsifiable liquid
Guarantee	Mustard seed powder (*Brassica hirta*) 10.89% (limits 10.35–11.43%) Sodium α-olefin sulfonate 6.91% (limits 6.56–7.26%)
Formulants	The product does not contain any USEPA List 1 formulants or formulants known to be TSMP Track 1 substances.
Container material and description	High-density polyethylene container, 4 L, with a screw-top opening
Specific gravity	1.034
pH of 1% dispersion in water	7.22
Oxidizing or reducing action	N/A
Storage stability	Stable for 29 days at 54°C ± 2°C and for one year at 20°C ± 2°C
Explodability	Not explosive

1.3 Details of Uses and Further Information

EXIT™ ISP, containing a combination of mustard seed powder (*Brassica hirta*) and sodium α-olefin sulfonate at 17.8%, is proposed for use as a commercial class product to control Richardson's ground squirrel in Canada, and Richardson's and Wyoming ground squirrel in the United States. When applied according to label directions, the mode of action of this product is by asphyxiation. Before application, a "field solution" must be prepared by diluting EXIT™ Concentrate Rodenticide with water at a ratio of 1:24 (4 L of concentrate to 96 L of water). Before treatment, a perforated cone must be placed in the burrow entrance. The field solution is then applied, using an aspirating foam nozzle (rated at approximately 11 L per minute), through the perforated cone until the burrow system appears to be full of foam (i.e., until foam begins to spill out of the burrow opening back through the cone). In the event that there is more than one opening to a burrow system, similar cones are to be placed in all burrow entrances within five metres of the burrow entrance to be treated, or into any burrow entrances suspected of being connected to the burrow entrance to be treated.

2.0 Methods of Analysis

2.1 Analytical Methods for Analysis of the Active Substance as Manufactured

Based on the nature of this product, the requirement of the analytical methods for the determination of the two active ingredients (a.i.) has been waived.

2.2 Analytical Methods for Formulation Analysis

Based on the nature of this product, the requirement of the enforcement analytical method has been waived.

3.0 Impact on Human and Animal Health

3.1 Integrated Toxicological Summary

The integrated system product EXIT™ ISP and associated end-use product EXIT™ Concentrate Rodenticide contain two components, which together have been characterized as active ingredients: food-grade mustard seed powder (MSP 10.89%) and sodium α-olefin sulfonate (AOS 6.91%). Since mustard seed powder is a food grade commodity, it was exempt from registration under the *Federal Insecticide, Fungicide and Rodenticide Act* in the United States; the USEPA required no data to assess the toxicological hazard of this active ingredient. The PMRA concurred with the USEPA on this matter and no data were reviewed for the mustard seed powder. The product contains other inert ingredients, not considered to be of toxicological concern. As such, the current toxicological assessment focussed on the AOS component of the ISP, as it was the only ingredient with unknown toxicological properties.

Sodium α-olefin sulfonates are long-chain sulfonic acids which are used in cosmetics, beauty products, surfactants or cleansing agents. Data sources submitted to the Agency include the following:

- complete acute studies for review and evaluation;
- articles from open literature;
- an assessment by the Cosmetic Ingredient Review Expert Panel;
- an assessment by the Soap and Detergent Association; and
- a review of the World Health Organization (WHO) Environmental Health Criteria No 169, *Linear Alkylbenzene Sulfonates and Related Compounds*.

The Agency does not have access to the studies that support the assessments by the Cosmetic Ingredient Review Expert Panel, the Soap and Detergent Association and the World Health Organization.

Most of the submitted data on AOS were in the form of literature citations or published monographs instead of complete animal studies. Many of the data elements were of limited quality. The hazard identification and risk assessment were based on the overall weight of evidence provided from the submitted data as well as consideration of its use in cosmetics, beauty products, surfactants or cleansing agents.

AOS surface-active agents are found in shampoos, bath and shower products, facial cleansing foams, dishwashing products, household cleaners and laundry detergents. Health and beauty products may contain AOS at levels between 3.6 (facial cleansing foams) and 16% (shampoo) of the total formulation. No serious injuries or fatalities have been reported following accidental ingestion of this surfactant by humans, according to the report from the Cosmetic Ingredient Review Expert Panel (1998).

Results of metabolism studies suggest no accumulation of AOS occurs and AOS is rapidly absorbed, metabolized and excreted following oral or dermal application. However, the absorption through the oral route of exposure is considered to be much greater than through the dermal route.

Sodium α-olefin sulfonate is of low toxicity by the oral and dermal routes of exposure, and is expected to be of low toxicity by inhalation. Inhalation and oral exposures are expected to be low. The product is corrosive to the eyes, is moderately irritating to the skin and is not considered to be a dermal sensitizer.

EXIT™ Concentrate Rodenticide is of low toxicity by the oral, dermal and inhalation routes of exposure. The product is corrosive to the eyes, is slightly irritating to the skin and is considered to be a dermal sensitizer.

Following repeated oral or dermal dosing in rats and mice, no adverse effects were reported in a number of studies. Increased liver weight and decreased kidney weights were observed in oral and dermal studies, respectively. These effects were not considered toxicologically significant effects because there were no associated histopathological findings. Thus, no significant systemic toxicity was observed in the subchronic feeding

studies in rats at doses up to 1000 mg/kg/day or in the carcinogenicity feeding study in rats at doses up to 195 or 259 mg/kg/day in males and females respectively.

There was no evidence of systemic toxicity reported in subchronic dermal studies in rabbits or in chronic dermal studies in mice.

There was no evidence of carcinogenicity in mice or rats following chronic exposure by either dermal or oral exposure to AOS. Available genotoxicity studies were negative, with one exception. In this instance, the study protocol was deemed to have been deficient, and when the study was repeated with an appropriate protocol, a negative response was elicited. The overall weight of evidence supports the contention that AOS is not a carcinogen. This position is currently expressed in published documents from the WHO, the Cosmetic Ingredient Review Expert Panel and the Soap and Detergent Association.

No maternal or developmental toxicity was noted in a study conducted in rats up to the highest dose tested, 600 mg/kg bw/day. Developmental toxicity was observed at or above maternally toxic doses (300 mg/kg/day or above) in mice, and rabbits. In mice, dams displayed clinical signs of toxicity and had reduced body-weight gains at doses that caused total litter loss and an increase in incidence of cleft palate in pups. In rabbits, maternal toxicity was evident as mortality, reduced body-weight gains and clinical signs of toxicity. Pups were found to have minor skeletal variations at this maternally toxic dose. The maternal toxicity is the most likely cause of fetal deaths and skeletal variations seen in these studies.

3.2 Determination of Acceptable Daily Intake

Not applicable.

3.3 Acute Reference Dose

Not applicable.

3.4 Toxicological Endpoint for Assessment of Occupational and Bystander Risks

For short- and intermediate-term occupational exposures via the dermal and inhalation routes, the mouse and rabbit developmental toxicity studies for AOS with a lowest observed adverse effect level (LOAEL) of 300 mg/kg bw/day were selected for use in the risk assessment. These studies identify the most serious endpoints of concern for mitigation. The no observed adverse effect level (NOAEL) for the studies was 2 mg/kg bw/day. This NOAEL (in mice) was based on clinical signs of toxicity, reduced body-weight gains at doses that caused total litter loss and resorptions as well as an increase in incidence of cleft palate in pups. In rabbits, maternal toxicity was evident as mortality, reduced body-weight gains, litter loss and clinical signs of toxicity. Pups were found to have minor skeletal variations at this maternally toxic dose. As the dose selection was

considered inappropriate, the LOAEL of 300 mg/kg bw/day is proposed to be used for risk assessment, with a target margin of exposure (MOE) of 1000. This MOE is derived from the standard 10 (interspecies) and 10 (intraspecies) uncertainty factor (UF), plus the addition of a 10 UF/SF (safety factor). Several factors were incorporated to justify the need for the additional UF/SF, including the following:

- database quality including the absence of a multigeneration reproduction study;
- severity of endpoint at the LOAEL of the study used in the risk assessment; and
- use of a LOAEL for risk assessment.

The developmental studies are considered appropriate for all durations of exposure; they are the only studies in the database that identify systemic toxicity endpoints. Other long-term studies exist in the database; however, there were no endpoints of concern on which to base a risk assessment. As well, mice appear to be the most sensitive species, further supporting the use of this study for regulatory purposes.

The toxicity seen in the developmental studies (gavage dosing) is probably due to bolus administration (i.e., gavage) of the chemical. This is further supported by the fact that no significant systemic toxicity was observed in feeding (oral) subchronic and chronic studies in rats or mice. The maternal and fetal deaths would not be expected to occur via the dermal route, which is the anticipated route of exposure because systemic toxicity was not observed in subchronic and chronic dermal toxicity studies. Similarly, a dermal developmental toxicity study conducted in mice demonstrated no toxicity to dams or pups, up to a dose approximating the limit dose, (dose calculated by reviewer) administered during gestation days 0–14. The lack of toxicity in the dermal study at a dose several times higher than the dose causing toxicity via the oral route of exposure supports the contention that dermal absorption is low; therefore, use of an oral study in the risk assessment may be conservative. There was no sensitivity to the young noted in several developmental studies; however, a key study (multigeneration reproduction) was not available to allow a more comprehensive assessment of reproductive parameters.

In light of the overall quality and limitations of the database, it was considered prudent to select the oral developmental toxicity endpoints for the risk assessment.

3.5 Drinking Water Limit

Not applicable.

3.6 Impact on Human or Animal Health Arising from Exposure to the Active Substance or to Impurities Contained in it

3.6.1 Operators

EXIT™ Concentrate Rodenticide is an emulsifiable concentrate containing 10.89% mustard seed powder and 6.91% sodium α-olefin sulfonate (AOS). It is proposed for

commercial use for the control of Richardson's ground squirrels in rangeland, ornamental plantings, orchards, golf courses, parks, nurseries and non-crop rights of way. Burrows can be treated from the spring snow melt until hibernation begins in the summer. Applicators have the potential for intermediate-term dermal and inhalation exposure while mixing, loading and applying EXIT™ Concentrate Rodenticide. Before treatment, a perforated cone is placed into the burrow entrance. Application equipment consists of a modified hand-held hose-end sprayer connected to an electric pump. An aspirating foam nozzle is attached to the end of the hose to facilitate foaming action. The field solution is applied through the perforated cone in the burrow entrance until the burrow system appears to be full of foam (i.e., until foam begins to spill out of the burrow opening back through the cone). If no activity is observed after approximately three minutes, the cone is removed and the burrow entrance is filled with earth. Use of this product is in the geographic range of Richardson's ground squirrels, normally limited to southern Alberta, Saskatchewan and the extreme southwest of Manitoba.

A quantitative assessment for mustard seed powder was not required. Mustard seed powder is food grade and unlikely to have any adverse toxicology health effects. Mustard seed powder was exempt from registration under the *Federal Insecticide, Fungicide and Rodenticide Act* in the United States as it is a food-grade chemical. Any irritation properties, such as eye or dermal irritation, can be mitigated through the use of protective equipment including goggles, one layer of clothing plus boots and gloves.

Quantitative exposure and risk assessments were conducted for AOS based on the Pesticide Handlers Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. To estimate exposure, appropriate subsets were created from the low-pressure handwand mixer/loader/applicator database file of the PHED. All data were normalized for kilogram of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. Dermal and inhalation exposure estimates were generated by coupling PHED data with the amount of active ingredient handled per day and normalizing by body weight. Operators could handle up to 8 kg of AOS per day when treating 1000 burrows with approximately 3.5 L of field solution per burrow. The exposure estimates are based on a clothing scenario of pants, a long-sleeved shirt and gloves being worn while mixing, loading and applying EXIT™ Concentrate Rodenticide.

Dermal Absorption

A dermal absorption value is required because an appropriate hazard endpoint from a dermal toxicity study is not available for use in the risk assessment. Based on the weight of evidence from an in vivo rat dermal absorption study, the physical-chemical properties of AOS, and the lack of systemic toxicity demonstrated in dermal toxicity studies, a 10% default dermal absorption value was selected for use in the exposure and risk assessment.

Dermal absorption was measured following a 0.5 mL application of 0.2% ^{14}C-AOS solution to the dorsal skin of rats. Test animals were sacrificed 24 hours following application to intact skin and 30 hours following application to damaged skin (in which the *stratum corneum* was removed prior to application of the test material). The solution was allowed to dry naturally, and there was no skin wash prior to sacrifice. ^{14}C-AOS was quantified in the brain, lung, liver, kidney, spleen, urine and bile. Approximately 0.6% of the applied dose was recovered from the intact skin test group after 24 hours. Several guideline deficiencies were noted including lack of quantification of AOS in the skin (including the administration site), blood, feces and cage wash; lack of protection of the administration site; lack of confirmation of applied dose; and lack of reporting of the test vehicle and individual data. Based on the study limitations, a quantitative estimate of dermal absorption could not be determined; however, dermal absorption of AOS is expected to be low.

A low dermal absorption potential is further supported by the physical chemical properties of the active ingredient. AOS is only available in the form of dissolved salts in aqueous solutions. In this form, AOS does not thermodynamically favour solubility in lipids and is, thus, unlikely to partition into the *stratum corneum*. Although a comparison to oral toxicity could not be made, there was no systemic toxicity at doses up to 100 mg/kg/day (highest dose tested) in the subchronic dermal toxicity study conducted in rabbits and in mice and rats up to 78 mg/kg/day (highest dose tested) in dermal carcinogenicity studies.

Mixer, Loader, Applicator Exposure and Risk Assessment

Dermal and inhalation exposure values were combined and coupled with the LOAEL of 300 mg/kg/day from the oral mouse and rabbit developmental studies. The MOE exceeds the target MOE of 1000, outlined in the table below.

Table 3.6.1.1 Mixer, Loader, Applicator Exposure and Risk Assessment

Scenario	Dermal UE µg/kg Handled[a]	Dermal Exposure µg/kg/d[b]	Inhalation UE µg/kg Handled[a]	Inhalation Exposure µg/kg/d[c]	Systemic Exposure µg/kg/d	MOE[d]
Mixer/loader/applicator 8 kg AOS day with low-pressure handwand sprayer	943	11	45	5.4	16.4	18 000

[a] Best-fit unit exposure (UE) values from the low-pressure handwand liquid mixer/loader/applicator PHED data set

[b] Where exposure = (PHED unit exposure in µg a.i. exposure/kg a.i. handled × 8 kg a.i. handled/day × 10% dermal absorption)/70 kg

[c] Where exposure = (PHED unit exposure in µg a.i. exposure/kg a.i. handled × 8 kg a.i. handled/day)/70 kg

[d] Where MOE = NOAEL/exposure, based on a LOAEL of 300 mg/kg/day from mouse and rabbit developmental studies

Risks to operators applying EXIT™ Concentrate Rodenticide for the control of ground squirrels are considered to be acceptable. The end-use product is a severe eye irritant; however, exposure to eyes is mitigated through the requirement of protective eye wear (goggles, face shield or safety glasses).

3.6.2 Bystanders

EXIT™ Concentrate Rodenticide is proposed for use in rangeland, ornamental plantings, orchards, golf courses, parks, nurseries and non-crop rights of way. The burrow entrance is closed following application of the foam by filling with earth and tamping firmly. The potential for postapplication exposure to bystanders is considered to be negligible.

3.6.3 Workers

There are no re-entry activities associated with EXIT™ Concentrate Rodenticide and a worker assessment is not required.

4.0 Residues

Not applicable.

5.0 Fate and Behaviour in the Environment

5.1 Physical and Chemical Properties Relevant to the Environment

A waiver was requested for the requirement for data on the physicochemical properties of MSP. MSP is a complex mixture (not a distinct chemical entity) and is a naturally occurring substance derived from the white mustard plant *Brassica hirta*. The waiver request was accepted.

The applicant also requested a waiver of the requirement for laboratory studies on the physicochemical properties of AOS. The rationales provided to accompany the waiver request for each physicochemical property are as follows.

Water Solubility
The water solubility of AOS is known to be > 0.7 g/mL (> 7.0×10^5 ppm), which indicates that AOS is very soluble in water (Cohen et al. 1984). A precise value was not provided. The applicant stated that a precise determination of the solubility of AOS in water is not needed to evaluate its potential mobility in soil. The waiver request was accepted.

Vapour Pressure
The vapour pressure of the aqueous solution in which AOS is dissolved will be affected by the presence of AOS, but the only component that will evaporate from the mixture is

water. AOS is a sodium salt of a sulfonic acid and, whether dissolved in water or not, will have no appreciable vapour pressure. No data on the vapour pressure of AOS are available. In addition, the product will be applied to subsurface burrows in limited areas only; thus, a determination of vapour pressure would not be useful in evaluating the environmental fate of AOS. This waiver request was accepted.

Henry's Law Constant
The product will be applied to subsurface burrows in limited areas only; thus, a determination of Henry's law constant would not be useful in evaluating the environmental fate of AOS. The waiver request was accepted.

***n*-Octanol–Water Partition Coefficient**
AOS is highly polar and highly water soluble. It dissociates completely in aqueous solution. Therefore, AOS has no appreciable tendency to partition from water into non-polar substrates such as octanol or fatty tissues. The waiver request was accepted.

Dissociation Constant
AOS is the salt of a strong base (NaOH) and a strong acid (α-olefin sulfonic acid). The sulfonate portion of AOS will be present at any pH normally encountered in the environment because sulfonic acid anions have almost no tendency to protonate. Thus, AOS will be present in the dissociated form at environmentally relevant pHs. The waiver request was accepted.

5.2 Abiotic Transformation

Not applicable.

5.3 Biotransformation

Biotransformation is expected to be an important transformation pathway for AOS in both terrestrial and aquatic systems. Based on soil studies using linear alkylbenzene sulfonate, a structurally similar anionic surfactant, AOS is expected to biotransform in soils. It is difficult to estimate the half-life of AOS in natural soil systems because some studies used nutrient-enriched, sludge-amended soils. One study that used unamended soils measured half-lives for linear alkylbenzene sulfonate in the range of 1.1–3.7 days, suggesting that linear alkylbenzene sulfonate and, by extrapolation, AOS would not be persistent in soil (Goring et al. 1975). In aquatic systems, AOS biotransforms rapidly (>90% primary biotransformation within 2–5 days in river and seawater). Thus, AOS is non-persistent in aquatic environments (McEwen and Stephenson 1979). Biotransformation of AOS is initiated by omega-oxidation or desulfonation, resulting in a carboxylated transformation product; this is subject to further degradation by beta-oxidation, which involves successive losses of two-carbon units leaving carboxylated intermediates. Biotransformation of AOS and its transformation products is expected to proceed to completion, with formation of biomass, carbon dioxide, water, and liberation of sulfate.

5.4 Mobility

The potential for leaching of the active constituents (AOS and MSP) into groundwater is expected to be low. Application will be made only to active, dry burrows, which are closed with soil following treatment. AOS is expected to biotransform in the soil after application. In the event that water enters the burrow, there is a potential for leaching of AOS to occur; however, the rapid biotransformation of AOS in aquatic systems would prevent its accumulation in groundwater. MSP has virtually no solubility in water and is, thus, expected to remain as a solid within a treated burrow, where it will be subject to biotransformation. No movement of MSP into groundwater is expected to occur under any conditions.

5.5 Dissipation and Accumulation under Field Conditions

Not applicable.

5.6 Bioaccumulation

The potential for bioaccumulation of the active constituents of EXIT™ Concentrate Rodenticide by non-target terrestrial and aquatic organisms is expected to be minimal because the proposed use pattern of EXIT™ Concentrate Rodenticide limits the potential for exposure to non-target terrestrial and aquatic organisms. Moreover, AOS is highly polar and highly water soluble, and has no appreciable tendency to partition from water into non-polar substrates such as octanol or fatty tissues. Thus, it is not expected that AOS will bioaccumulate in the tissues of non-target organisms.

5.7 Summary of Fate and Behaviour in the Terrestrial Environment

The main route of transformation of AOS in the terrestrial environment is expected to be biotransformation in soil under aerobic conditions. It is difficult to predict the half-life of AOS in soil; however, the available data from soil biotransformation studies and from a field environmental fate study (all using linear alkylbenzene sulfonate, a structurally similar anionic surfactant) suggest that AOS is not likely to be persistent in soil. Biotransformation of AOS and its transformation products is expected to proceed to completion, with formation of biomass, carbon dioxide, Water, and liberation of sulfate. MSP is also expected to be readily metabolized by soil micro-organisms to produce carbon dioxide and nutrients available for uptake by micro-organisms. Neither AOS nor MSP is expected to accumulate in soil.

Based on the proposed use pattern of EXIT™ Concentrate Rodenticide, the potential for leaching of AOS and MSP into groundwater is expected to be low. Application will be made only to active, dry burrows, which are closed with soil following treatment. AOS is expected to biotransform in the soil after application. In the event that water enters the burrow, there is a potential for leaching of AOS to occur; however, the rapid biotransformation of AOS in aquatic systems would prevent its accumulation in

groundwater. MSP has virtually no solubility in water and is, thus, expected to remain as a solid within a treated burrow, where it will be subject to biotransformation. No movement of MSP into groundwater is expected to occur under any conditions. Neither AOS nor MSP is expected to accumulate in groundwater.

5.8 Summary of Fate and Behaviour in the Aquatic Environment

Based on the proposed limited use pattern of EXIT™ Concentrate Rodenticide, the expected biotransformation of AOS in soil and the expected low potential for leaching of the active constituents to groundwater, it is not expected that AOS or MSP will enter into aquatic environments. It is very unlikely that AOS or MSP will reach surface water through runoff or spray drift. In the event that leaching of AOS to groundwater does occur, AOS is expected to biotransform rapidly based on results from biotransformation studies using river and seawater. AOS is expected to be non-persistent in aerobic aquatic systems. Biotransformation of AOS and its transformation products is expected to proceed to completion, with formation of biomass, carbon dioxide, water, and liberation of sulfate.

5.9 Expected Environmental Concentrations

Expected environmental concentrations (EECs) of the two active constituents, AOS and MSP, in soil, aquatic systems, vegetation and other food sources as well as drinking water cannot readily be calculated because of the product application method. The application instructions indicate that the product is to be applied into a burrow entrance until the burrow is completely full of foam; therefore, application will be below the soil surface and only in spot locations, and the amount of product applied may vary. The active constituents are not expected to contaminate aquatic systems, vegetation, other food sources or drinking water. Furthermore, no studies on the environmental toxicology of AOS or MSP were provided (a waiver was requested from these data requirements and accepted by the PMRA). In the absence of environmental toxicology data, a quantitative assessment of the risk to non-target terrestrial and aquatic organisms cannot be conducted; thus, expected environmental concentrations are not required.

The input of AOS and MSP into the environment is very limited from use of EXIT™ Concentrate Rodenticide, particularly in comparison to existing environmental inputs. MSP is a natural product of native botanical origin and a food ingredient; use of this product will release only small amounts of MSP in limited underground areas. AOS has been widely used for decades in personal care products, especially dishwashing liquids and shampoos. Such products enter domestic and commercial wastewater and are discharged to the environment. AOS is also a component of many fire-suppressant foams that are applied in large volumes to forests, woodlands and grasslands to combat wildfires. Moreover, AOS is widely used as a direct additive to soil and groundwater in remediation programs for organic contaminants. Finally, AOS is widely used throughout the world in tertiary oil recovery. Water containing AOS is pumped underground to serve as a release agent and carrier for oil that cannot be recovered by other means. As a result

of all these uses, AOS already enters the environment in large quantities. In contrast, the use of EXIT™ Concentrate Rodenticide would result in release to the environment of relatively small quantities of AOS, underground and in limited areas.

6.0 Effects on Non-target Species

The applicant requested a waiver of the requirement for data from laboratory studies on effects on the following non-target terrestrial and aquatic organisms.

Terrestrial

- invertebrates
- birds
- mammals
- plants

Aquatic

- invertebrates
- fish

The waiver request was accepted by the USEPA. The PMRA concurs with the USEPA regarding the waiver request and believes that the intended use of this product would present a low risk to aquatic invertebrates, fish and plants as well as terrestrial invertebrates, birds, plants and mammals. Some concerns were identified regarding risks to vulnerable, threatened and endangered species that inhabit burrows in the areas where ground squirrels live. These concerns are further discussed in Section 6.4.

6.1 Effects on Terrestrial Organisms

Not applicable.

6.2 Effects on Aquatic Organisms

Not applicable.

6.3 Effects on Biological Methods of Sewage Treatment

Not applicable.

6.4 Risk Characterization

The mode of action of EXIT™ Concentrate Rodenticide is to cause the target organism (i.e., the ground squirrel) to asphyxiate following application of a sufficient amount of the product to completely fill the burrow. Any organism within the burrow at the time of application will, therefore, be killed. Thus, the proposed use of EXIT™ Concentrate Rodenticide poses a risk of unintentionally killing non-target terrestrial organisms that inhabit or use burrows. Examples of such non-target organisms include rats, mice, ferrets, voles, chipmunks, squirrels (other species), badgers, weasels, groundhogs, prairie dogs, snakes, toads, frogs, burrowing owls and swift foxes. The Committee on the Status of Endangered Wildlife in Canada (COSEWIC) has identified the following species that inhabit or use burrows as species at risk.

- Ord's kangaroo rat *(Dipodomys ordii)*—special concern in Alberta and Saskatchewan
- Black-tailed prairie dog *(Cynomys ludovicianus)*—special concern in Saskatchewan
- Northern leopard frog *(Rana pipiens)*—special concern in Alberta, Saskatchewan, Manitoba
- Great plains toad *(Bufo cognatus)*—special concern in Alberta, Saskatchewan, Manitoba
- Burrowing owl *(Athene cunicularia)*—endangered in Alberta and Saskatchewan
- Swift fox *(Vulpes velox)*—endangered in Alberta and Saskatchewan

The burrowing owl is an endangered species that is of particular concern because burrowing owls use abandoned ground squirrel burrows for nesting, roosting, shelter and escape from predators. Protective measures are necessary to minimize the risk of unintentional kills of non-target terrestrial organisms, particularly species that are of special concern, threatened or endangered species.

6.5 Risk Mitigation

To minimize the risk of accidental kills of non-target organisms, including species at risk, measures must be taken to ensure that the product is applied only to burrows occupied by Richardson's ground squirrels. As it is difficult for an untrained individual to recognize the signs of the presence of a burrowing owl or other species at risk inside a burrow and to know the occupied habitat of species at risk, the following statements, which will help to mitigate the risks to non-target organisms, must appear on the product label:

> APPLY TO BURROWS OCCUPIED BY ONLY RICHARDSON'S GROUND SQUIRRELS. DO NOT APPLY TO UNOCCUPIED BURROWS.

The following measures are necessary to minimize the risk of unintentional kills of non-target organisms, including species at risk (e.g., burrowing owl [*Athene cunicularia*]; swift fox [*Vulpes velox*]). Applicators of EXIT™ Concentrate Rodenticide should observe the potential treatment area before treating burrows to confirm the presence of Richardson's ground squirrel activity and to ensure there is no evidence of species at risk activity or presence in burrows.

For information on species at risk in your area, contact your provincial or federal wildlife officials.

In addition, the following label statement is required to minimize the potential for aquatic exposure:

DO NOT contaminate irrigation or drinking water supplies or aquatic habitats (such as lakes, rivers, sloughs, ponds, prairie potholes, creeks, marshes, streams, reservoirs, ditches and wetlands) by cleaning of equipment or disposal of wastes.

7.0 Efficacy Data and Information

7.1 Effectiveness

7.1.1 Intended Use

EXIT™ Concentrate Rodenticide, containing a combination of mustard seed powder (*Brassica hirta*) and sodium α-olefin sulfonate at 17.8%, is proposed for use as a commercial class product to control Richardson's ground squirrel in Canada. When applied according to label directions, the mode of action of this product is by asphyxiation. Before application, a "field solution" must be prepared by diluting EXIT™ Concentrate Rodenticide concentrate with water at a ratio of 1:24 (4 L of concentrate to 96 L of water). Before treatment, a perforated cone must be placed into the burrow entrance. The field solution is then applied, using an aspirating foam nozzle (rated at approximately 11 L per minute), through the perforated cone until the burrow system appears to be full of foam (i.e., until foam begins to spill out of the burrow opening back through the cone). In the event that there is more than one opening to a burrow system, similar cones are to be placed into all burrow entrances within five metres of the burrow entrance to be treated, or into any burrow entrances suspected of being connected to the burrow entrance to be treated.

7.1.2 Mode of Action

The mode of action of EXIT™ Concentrate Rodenticide is by asphyxiation. The mustard seed powder reportedly acts as a respiratory irritant, thereby increasing the rate of uptake of the sodium α-olefin sulfonate foam by the ground squirrels and decreasing the time until death.

7.1.3 Effectiveness Against Pest

7.1.3.1 Description of Pest Problem

The Richardson's ground squirrel (*Spermophilus richardsonii* (Sabine)), commonly called the gopher, prairie gopher, yellow gopher, flickertail, or picket pin, occurs in the Prairies (southern regions of Alberta and Saskatchewan and southwestern region of Manitoba). Richardson's ground squirrels eat a wide variety of grasses and broad-leaved plants. They can cause direct productivity losses in crops (e.g., cereals) and may also compete with livestock for forage. The mounds of soil excavated from burrows can smother desired vegetation and damage farm machinery. In addition, ground squirrels are an important food source for badgers, which in turn can cause damage to crops and pastures through their burrowing activity (Alberta Agriculture 1984).

According to Alberta Agriculture, Food and Rural Development (AAFRD), Richardson's ground squirrels spend the majority of their life underground, with many activities (e.g., mating, raising litters) taking place within the burrows. Both males and females are reproductively mature the year following their birth. Mating occurs only in spring, shortly after females emerge from hibernation. Each spring, a female can produce one litter. Juveniles first begin to appear above ground when they are four weeks old. They immediately begin eating solid food and rapidly become nutritionally independent of their mother. Litter size often varies with the quality of vegetation, averaging between 5 and 6 on native pasture and 9 and 10 on tame forage crops. During June and July, most of the young ground squirrels seek new areas to establish colonies. Females live their entire life in the burrow in which they were born or near their birth site, while males of the year tend to disperse after weaning (up to 3 km away). Natural mortality among Richardson's ground squirrels is high, particularly among males, with the major cause of death being predation and starvation. The average life span of a female is four years, whereas a male usually lives for only a year. Richardson's ground squirrels hibernate during the winter, with adult males entering hibernation some time in late July. Females enter hibernation several weeks later, followed by juveniles. Each animal hibernates alone in a special chamber (called the hibernaculum), which is sealed with a soil plug. Males emerge from hibernation from late February to mid March, while females come out a few weeks later.

7.1.3.2 Efficacy Trials

Three field trials were submitted to evaluate the efficacy of EXIT™ Concentrate Rodenticide (containing a combination of mustard seed powder and sodium α-olefin sulfonate at 17.8%) to control ground squirrels. Two studies were conducted using Richardson's ground squirrels and one study was conducted using Wyoming ground squirrels, a species closely related to the Richardson's ground squirrel (same genus, similar biology). In all cases, the EXIT™ Concentrate Rodenticide was mixed with water at a ratio of 1 part concentrate to 23–24 parts water (label dilution rate: 1:24 ratio). The resulting "field solution" was applied under pressure (11.4 L per minute nozzle) as a foam to active burrows to the point of overflow. A wire mesh was placed over the entrance of

the burrow before application to prevent resident ground squirrels from escaping. After treatment, the burrow entrances were packed with earth and monitored for activity.

The first study was conducted in Cochrane, Alberta, from April to May 1998. The experimental area consisted of two study sites with active Richardson's ground squirrel burrows. Both sites (0.75 ha range pasture and 0.13 ha alfalfa field) were treated. A 30-m wide buffer zone (also treated) was established at the same time around the treatment plots to prevent re-invasion of ground squirrels from other areas. At both sites, 99% of the active burrow openings were inactive after the initial treatment, as determined by closed burrow census. Any burrow systems found to be active after the initial treatment were re-treated. No animals were observed in the treatment areas during the post-treatment period.

The second study was conducted in Grand County, Colorado, in May 2000 using a population of Wyoming ground squirrels. The experimental area (dominant vegetation not specified) consisted of two census areas (0.8 ha and 0.5 ha). These census areas were surrounded by buffer zones (in some areas, 45 metres wide) that were also treated with EXIT™ Concentrate Rodenticide. The results did indicate that repeated treatments significantly reduced the numbers of active Wyoming ground squirrels (as assessed by both closed burrow and visual census methods).

The third study was conducted in Cochrane, Alberta, in June 2000. The experimental site (vacant grass field within town boundary) consisted of a 0.75 ha treatment area surrounded by a 1.5 ha buffer zone (also treated with EXIT™ Concentrate Rodenticide), and a 0.24 ha untreated area approximately 75 metres away from the treated site. The efficacy of EXIT™ Concentrate Rodenticide for controlling Richardson's ground squirrels was approximately 99% (days 1–3 post-treatment), as determined by closed burrow census, and 100% (first monitored on days 3–4 post-treatment), as determined by post-treatment visual census. Any burrow system found to be active after the initial treatment was re-treated.

Based on these three field studies, it can be concluded that EXIT™ Concentrate Rodenticide, when applied according to label directions, will control Richardson's ground squirrels by asphyxiation. Several modifications to the proposed label are recommended (e.g., use of inverted cones/pylons in any auxiliary burrow entrances that may be connected to the main burrow entrance being treated).

7.2 Observations on Undesirable or Unintended Side Effects on Beneficial and Other Non-target Organisms, Succeeding Crops, Other Plants or Parts of Treated Plants Used for Propagating Purposes (e.g., seed, cuttings, runners) (OECD 7.5)

No undesirable effects on crops were observed. Regarding non-target effects, refer to Section 6, Effects on Non-target Species.

7.3 Economics

The cost of using this product is difficult to estimate as it is not currently marketed. However, the applicant has speculated that the product may cost approximately $10 (Canadian) per litre of concentrate. Based on information provided in one of the efficacy studies submitted in support of the application to register EXIT™ Concentrate Rodenticide, 3.38 L of "field solution" are required, on average, to treat a Richardson's ground squirrel burrow. Given that 1 L of concentrate makes 25 L of field solution, the cost of treating a typical burrow would be approximately $1.35 (Canadian). Cost per hectare would depend on ground squirrel density. Invasion pressures from surrounding areas would require repeat applications in areas adjoining untreated and infested sites, which would add to the cost of treatment. Although the cost of treatment per ground squirrel burrow using EXIT™ Rodenticide will presumably be greater than the cost of using conventional baits, there is probably a niche in the market for this product, which has such a high level of efficacy.

7.4 Sustainability

7.4.1 Survey of Alternatives

7.4.1.1 Non-chemical Control Practices

According to AAFRD, some data indicate that the strategic planting of tall vegetation stands may encourage ground squirrels to move away from cultivated areas to more open grass fields. In addition, the use of raptor (hawk and owl) nest boxes and perches close to ground squirrel colonies may reduce rodent numbers and limit colony growth. Other non-chemical control practices include trapping, shooting and destroying burrows, all of which are labour intensive. Trapping is only recommended for reducing low to moderate squirrel populations over relatively small acreages or where chemical control methods are inappropriate. Shooting may be an option (if local laws permit), especially when ground squirrel numbers are low. Finally, ripping up old burrow sites, in areas where ground squirrels have already been removed, may reduce the rate of re-invasion.

7.4.1.2 Chemical Control Practices

Products currently registered for ground squirrel control include anticoagulants (i.e., chlorophacinone and diphacinone) and non-anticoagulant toxicants (i.e., strychnine, zinc and phosphide). All of these products are available as ready-to-use (RTU) baits. In addition, chlorophacinone is registered in a liquid concentrate form to be used in the formulation of fresh bait. Fumigation devices containing sulphur are also registered for this use.

7.4.2 Compatibility with Current Management Practices, Including Integrated Pest Management

Data have not been submitted to indicate what contribution EXIT™ Concentrate Rodenticide could make to an integrated pest management program. However, it could contribute to a program that includes baits. Optimal bait consumption usually occurs early in the season, before green vegetation is available as an alternate food source. For this reason, even though EXIT™ Concentrate Rodenticide can be used throughout the ground squirrel season, it may be especially of value for late season control. Because the EXIT™ Concentrate Rodenticide method of ground squirrel control may be more labour intensive and costly than other methods involving baits, its use may be limited to relatively small areas or spot treatments in larger areas. Once control is achieved in targeted areas, the area of treatment could be expanded.

7.4.3 Contribution to Risk Reduction

The contribution to risk reduction was not assessed in the context of value.

7.4.4 Information on the Occurrence or Possible Occurrence of the Development of Resistance

As per Regulatory Directive DIR99-06, *Voluntary Pesticide Resistance-Management Labelling Based on Target Site/Mode of Action*, a resistance management statement would normally be recommended on the label of a commercial class product. However, such a statement is not appropriate for this product. Resistance to EXIT™ Concentrate Rodenticide is unlikely to occur as the mode of action is by asphyxiation.

7.5 Conclusions

Based on the submitted studies, it can be concluded that EXIT™ Concentrate Rodenticide will control Richardson's ground squirrels by asphyxiation, when applied according to label directions. The label states that 4 L of EXIT™ Concentrate Rodenticide are to be diluted with 96 L of water and applied under pressure through an aspirating foam nozzle at a rate of 11.4 L per minute so that the resultant foam fills the burrow system (burrow entrances are to be blocked). Although the submitted efficacy trials were conducted using a mesh basket through which the treatment was applied into each active burrow, an inverted perforated cone/pylon is an acceptable substitution, provided that the perforations are of an appropriate size so as not to impede the foam from entering the burrow. Repeat applications may be required depending on invasion pressures from surrounding areas.

8.0 Toxic Substances Management Policy

During the review of AOS, MSP and the EXIT™ ISP, the PMRA has taken into account the federal Toxic Substances Management Policy[1] and has followed its Regulatory Directive DIR99-03[2]. It has been determined that these products do not meet TSMP Track 1 criteria for the following reasons:

- MSP is not predominantly anthropogenic because it is a natural product derived from the white mustard seed plant *Brassica hirta*.
- No data are available regarding the persistence, bioaccumulation potential or toxicity of MSP.
- AOS is a substance that results from human activity; thus, it is anthropogenic.
- AOS does not meet the criteria for persistence. Its value for half-life in water (< 5 days) is below the TSMP Track 1 cut-off criteria for water (≥ 182 days). Biotransformation data for a structurally similar anionic surfactant, linear alkylbenzene sulfonate, suggest that the half-life of AOS in soil is expected to be in the range of 1–26 days, which is below the TSMP Track 1 cut-off criteria for soil (≥ 182 days). No data are available regarding the half-life of AOS in air or in sediment.
- While no bioaccumulation factor, bioconcentration factor or log K_{ow} data are available for AOS, this substance is not expected to bioaccumulate. AOS is very soluble in water (> 0.7 g/mL) and highly polar; thus, it is not expected to partition from water into biological tissues.
- Neither AOS nor MSP is known to form any major transformation products that meet the TSMP Track 1 criteria.
- Neither AOS nor MSP contains any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

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1 The federal Toxic Substances Management Policy is available through Environment Canada's website at www.ec.gc.ca/toxics.

2 Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*, is available through the Pest Management Information Service. Phone: 1 800 267-6315 within Canada or (613) 736-3799 outside Canada (long distance charges apply); Fax: (613) 736-3798; E-mail: pmra_infoserv@hc-sc.gc.ca; or through our website at www.pmra-arla.gc.ca

The formulated product does not contain any USEPA Inert List 1 or 2 formulants or any known TSMP Track 1 substances.

9.0 Regulatory Decision

The PMRA has carried out an assessment of available information in accordance with the Pest Control Products Regulations and has found it sufficient to allow a determination of the safety, merit and value of the reduced-risk integrated systems product EXIT™ ISP and the associated end-use product EXIT™ Concentrate Rodenticide. The Agency has concluded that the use of EXIT™ ISP and the end-use product EXIT™ Concentrate Rodenticide in accordance with the label has merit and value consistent with the Pest Control Products Regulations and does not entail an unacceptable risk of harm. Based on the considerations outlined above, the use of EXIT™ ISP and the end-use product EXIT™ Concentrate Rodenticide for the control of Richardson's Ground Squirrels in rangeland, ornamental plantings, orchards, golf courses, parks, nurseries and non-crop rights of way in southern Alberta, Saskatchewan and southwestern Manitoba is proposed for full registration, pursuant to the Pest Control Products Regulations.

The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document to allow interested parties an opportunity to provide input into the proposed registration decision for this product.

List of Abbreviations

AAFRD	Alberta Agriculture, Food and Rural Development (formerly Alberta Agriculture)
a.i.	active ingredient
AOS	sodium α-olefin sulfonate
bw	body weight
CAS	Chemical Abstracts Service
CD	cesarian derived
ha	hectare
HDT	highest dose tested
ISP	integrated system product
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{ow}	octanol/water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
mg	milligram(s)
mL	millilitre(s)
MOE	margin of exposure
MSP	mustard seed powder
NOAEL	no observed adverse effect level
PHED	Pesticide Handlers Exposure Database
PII	primary irritation index
pK_a	dissociation constant for the acid form
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RBC	red blood cell
SF	safety factor
TSMP	Toxic Substances Management Policy
µg	micrograms
µL	microlitre
UE	unit exposure
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization

Appendix I Toxicology

METABOLISM: RAT (sodium α-olefin sulfonate)

After oral administration of AOS in rats, the level of radiolabel in blood reached a peak at 3 hours and then rapidly decreased. At 24 hours after administration, about 0.8% was detected in the caecal contents and < 0.02% in other tissues. No specific accumulation was observed in any tissue. Within 24 hours of administration, 72% of the dose was excreted in urine and 22% in feces. After four days, no ^{14}C residue was detected in urine or feces. Cumulative excretion in the bile within 12 hours after administration was about 4.3% of the radioactivity administered. As most of the ^{14}C-labelled compounds in urine were alcoholic, unsaturated and of sulfonic functionality, the metabolite may be a hydroxylated or polyhydroxylated sulfonic acid with a shorter chain than AOS, although the precise chemical structure remains to be elucidated. Results suggest no accumulation of AOS occurs and AOS is rapidly absorbed, metabolized and excreted.

Study Type	Species/Strain/Doses	LD_{50} (mg/kg bw)	Degree of Toxicity Significant Effects
ACUTE TOXICITY—sodium α-olefin sulfonate			
Oral	Rat (Sprague-Dawley) 5/sex; 5000 mg/kg bw Purity: 4.5% a.i.	LD_{50} = 2161 mg/kg males = 1895 mg/kg females	No label comments
Dermal	Rabbit	LD_{50} > 2020 mg/kg bw	No label comments
Eye Irritation C14-16 AOS	Rabbit (New Zealand White) 2 males, 4 females; 0.1 mL undiluted. Purity: 4.5% a.i.	The maximum irritation score was 26.8 at 48 hours and 15.5 at 7 days post-treatment.	Corneal opacity was present in 4/6 rabbits 7 days post-treatment. Conjunctival irritation was present in 5/6 rabbits 7 days post-treatment. **DANGER—CORROSIVE**
Dermal Irritation	Rabbit	Primary irritation index (PII) = 3.25 for intact and 3.42 for abraided skin (shallow lateral fissuring)	**WARNING—SKIN IRRITANT**
Dermal Sensitization (Buehler test)	Guinea Pig. C14-16 at 25% for induction, and 10 and 5% for challenge	Negative	
GENOTOXICITY			
In vitro mutagenicity AOS products (21–38% a.i.)	*Salmonella typhimurium* TA 98, 100, 1535, 1537, 1538 Doses: 2, 10 and 100 µg/plate; 10 000 ppm in reversion plate assay	Negative in 4 separate tests	
In vivo mutagenicity Host-mediated—rat AOS (28.4% a.i.)	*Salmonella typhimurium* TA 1530, 1534 Doses: 283 mg/kg	(+) in *Salmonella typhimurium* TA 1530 (-) in *Salmonella typhimurium* TA 1534 Positive response in TA1530 could be due to the following: a) incomplete ether extraction b) high pH 11.3—when adjusted to pH 8.5 with sulfuric acid yielded negative response.	

Study	Species(Strain)/Doses	NOAEL/LOAEL (mg/kg bw/day)	Significant Effects at Different Doses (mg/kg bw/day)/Comments
SUBCHRONIC AND CHRONIC TOXICITY: RAT			
One-week Feeding Study (1993) C14-16 AOS (70% C14: 30% C16)	Rats Doses: 0, 0.625%, 1.25% and 2.5% (0, 125, 250 and 300 mg/kg/day, respectively) for 7 days	NOAEL = 250 mg/kg/day LOAEL = 300 mg/kg/day	≥ 250: Non-adverse ↑ liver to body-weight ratios (males) 300: ↓ body-weight gain
90-day Feeding Study (1993) AOS (89.7% a.i.)	Rats Doses: 0, 40, 200 or 1000 mg/kg/day	NOAEL ≥1000 mg/kg/day (limit dose) LOAEL was not established	1000: increased liver to body weight ratio. Non-adverse
91-day Feeding Study (1993) C14-16 (34% a.i.)	Rats Doses: 0, 50, 150 or 500 mg/kg/day	NOAEL > 500 mg/kg/day LOAEL was not established	500: ↑ RBC, non-adverse
Chronic Feeding Toxicity/Carcinogenicity (1976) AOS	CFY rats Doses: 0, 1000, 2500 or 5000 ppm (0, 39, 96 or 195 mg/kg/day (males) and 0, 57, 132 or 259 mg/kg/day (females) for 104 weeks	NOAEL = 2500 ppm LOAEL = 5000 ppm	5000 ppm: ↓ body-weight gain in males and females. **No evidence of carcinogenicity**
Chronic Feeding Toxicity/Carcinogenicity	MRC Wistar rats Doses: 0, 500, 750 or 1000 ppm study terminated when mean survival reached 50%	NOAEL = 1000 ppm	No adverse effects reported up to the maximum treated dose
Chronic Toxicity—Dermal (70 weeks)	Wistar rats Daily applied 0.5 mL of 1.0, 10 or 30% AOS solution (assuming an average body weight of 200 g, doses = 0, 1, 10 or 30 mg/kg bw/day)	NOAEL ≥ 30 mg/kg bw/day. No adverse gross or histopathological findings were reported.	

Study	Species(Strain)/Doses	NOAEL/LOAEL (mg/kg bw/day)	Significant Effects at Different Doses (mg/kg bw/day)/Comments
Carcinogenicity Dermal (1993) Essentially hydrolyzed C14-16 and C16-18 AOS (30% a.i.) Partially hydrolyzed AOS (30.9% a.i.) + contains residual levels of sultone Commercial C14-16 AOS (38.9% a.i.)	Long Evans rats 50/sex/dose Doses: 1 mL/kg dermally applied twice a week for 2 years (assuming an average body weight of 200 g, doses = 0, 60, 62 or 78 mg/kg bw)	NOAEL > 78 mg/kg bw/twice a week.	Males treated with 60 mg/kg bw/twice a week had ↓ in absolute and relative to body kidney weights. In the absence of histopathological indications of toxicity the finding was not considered to be adverse. **No evidence of carcinogenicity**
SUBCHRONIC AND CHRONIC TOXICITY: MICE			
Carcinogenicity Dermal (1993) 20 or 25% C14-18 AOS 20 or 25% C14-16 AOS 6.7 or 8.3% C16-1,4-sultone	Mice Doses: 0.02 mL (in water or acetone) dermally applied 3 times a week for 92 weeks		No significant toxicity/histopathology attributable to treatment was found. No evidence of carcinogenicity
Study	**Species (Strain)/Doses**	**NOAEL/LOAEL (mg/kg bw/day)**	**Significant Effects at Different Doses (mg/kg bw/day)/Comments**
SUBCHRONIC TOXICITY: RABBIT			
90-day Dermal Toxicity (1993)	Rabbit Doses: 2 mL/kg/day of a 5% (100 mg/kg/day) aqueous solution of AOS (34% a.i.) for 90 days.	NOAEL = 100 mg/kg/day (HDT) LOAEL ≥ 100 mg/kg/day	100 mg/kg: mild to moderate skin irritation
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY			
Developmental Toxicity (1975) C14-18 AOS oral gavage	CD-1 mice 20/dose Doses: 0, 0.2, 2, 300 and 600 mg/kg/day on gestation days 6–15	**Maternal and Developmental Toxicity** **NOAEL** = 2 mg/kg/day **LOAEL** = 300 mg/kg/day	**Maternal** ≥ 300: pilo-erection, ↓ movement, ↓ body-weight gain litter loss (6/20); ↑ resorptions 600: deaths **Developmental** ≥ 300: cleft palate 600: ↓ body-weight gain and minor skeletal anomalies
Developmental Toxicity (1975) C14-18 AOS oral gavage	CD Rats. 20/dose Doses: 0, 0.2, 2, 300 and 600 mg/kg/day on gestation days 6–15	**Maternal and Developmental Toxicity** **NOAEL** ≥ 600 mg/kg/day (HDT) **LOAEL** not established	**Maternal and Developmental** No toxicity noted up to the limit dose

Study	Species(Strain)/Doses	NOAEL/LOAEL (mg/kg bw/day)	Significant Effects at Different Doses (mg/kg bw/day)/Comments
Developmental Toxicity (1975) C14-18 AOS oral gavage	NZW Rabbits. 13/dose Doses: 0, 0.2, 2, 300 and 600 mg/kg/day on gestation days 6–18	**Maternal and Developmental Toxicity** **NOAEL** = 2 mg/kg/day **LOAEL** = 300 mg/kg/day	**Maternal** ≥ 300: bw loss, mortality (1/13) litter loss; anorexia, diarrhea 600: mortality (13/13) **Developmental** 300: ↓ bw: ↑ incidence of minor skeletal anomalies and extra ribs
Developmental Toxicity AOS (Dermal)	CD-1 mice 0.5 mL of a 0.1, 1 or 5% solution applied to the skin of dams on days 0–14 of gestation	No adverse effects reported on dams, and no evidence of fetal toxicity. (Assuming a 500 mg weight for a 0.5 mL volume of solution, a 5% AOS solution would contain 25 mg of AOS, calculated on a w/w basis). Given an assumed female mouse body weight of 20 g (body weights were not reported in the text), the applied dose would be close to the limit dose for developmental toxicity studies.	
SPECIAL STUDIES			
Dermal Absorption (1977) AOS	Rat 3 males were administered 0.5 mL of a 0.2% solution of ^{14}C-AOS (specific activity 6.55 µCi/mg) was applied to the dorsal skin	Dermal absorption was determined to be extremely low based on recovery of a total of about 0.24% of the applied dose in major organs 24 hours following dosing. After 24 hours, 0.33% of the radiolabel was excreted in the urine and 0.08% in the bile. Limitations included lack of blood or skin-bound residue analysis.	
EXIT™ CONCENTRATE RODENTICIDE END-USE PRODUCT			
Acute Oral LD_{50}	Rat Groups of 5 male and 5 female rats were given a single oral dose of 5050 mg/kg	LD_{50} > 5050 mg/kg males/females	No label comments
Acute Dermal LD_{50}	Rabbit Groups of 5 male and 5 female rabbits were applied with a single dose of 2020 mg/kg to 10% clipped body surface area for 24 hours	LD_{50} > 2020 mg/kg males/females	No label comments
Acute Inhalation LC_{50}	Rat Groups of 5 male and 5 female rats were exposed nose only to aerosol concentration of 2.37 mg/L EXIT™ Concentrate Rodenticide for 4 hours	LC_{50} males and females: > 2.37 mg/L	No label comments required

Study	Species(Strain)/Doses	NOAEL/LOAEL (mg/kg bw/day)	Significant Effects at Different Doses (mg/kg bw/day)/Comments
Primary Eye Irritation	Rabbit 0.1 mL of EXIT™ Concentrate Rodenticide was instilled into the conjunctival sac of 1 male and 5 female rabbits; eyes were washed 24 hours after instillation		Initial and Persistent Opacity. Corneal opacity was not resolved by Day 21 **DANGER—CORROSIVE**
Primary Dermal Irritation	Rabbit Groups of (3 males and 3 females) rabbits were dermally exposed to 0.5 mL of EXIT™ Concentrate Rodenticide for 4 hours	The mean PII was 0.6	Slightly irritating. No label comments required
Skin Sensitization (Buehler Test)	Guinea pig		There was a 100% incidence of reaction to challenge with EXIT™ Concentrate Rodenticide Positive **Dermal sensitizer**

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