A method for treating a pre-cancerous skin lesion on a human subject with glyphosate is described, along with compositions for said treatment.
METHOD OF TREATING PRE-CANCEROUS LESION WITH GLYPHOSATE, AND COMPOSITIONS THEREOF

FIELD OF THE INVENTION

This invention is directed to the use of glyphosate compositions to treat pre-cancerous skin lesions.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of US Provisional Application No. 62/078,403, filed November 1, 2014, and entitled "METHOD OF TREATING PRE-CANCEROUS LESION", said provisions hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

Skin cancer is a common form of cancer, with thousands of people diagnosed and dying from it every year. Pre-cancerous lesions such as actinic keratosis may precede the formation and diagnosis of cancer of the skin, and cause discomfort and other problems.

Glyphosate is an effective but controversial herbicide, with environmentalists and other groups concerned in part with mild to moderate systemic and dermal toxicity reported from contact with glyphosate-containing compositions. Amerio et al., "Skin Toxicity from Glyphosate-Surfactant Formulation" J. Toxicology CLINICAL TOXICOLOGY 42(3):317-319 (2004).

A safe, efficacious treatment for pre-cancerous lesions would be beneficial.

BRIEF SUMMARY OF THE INVENTION

The present invention is directed to the use of glyphosate-containing compositions in the treatment of pre-cancerous skin lesions. A glyphosate composition is administered by directly, topically applying the composition to a lesion. The lesion disappears and appears to be fully cured within weeks or even days, such that the skin regains the appearance of adjacent, healthy skin. The present invention is also directed to a composition comprising glyphosate for the treatment of pre-cancerous skin lesions; and to the use of a composition comprising glyphosate, for the preparation of a medicament for the treatment of a pre-cancerous skin lesion.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method for treating a pre-cancerous lesion with glyphosate, comprising the step of topically applying the glyhosate to the lesion in a therapeutically effective amount.

The present invention is also directed to a composition comprising glyphosate for instance as discussed above, for the treatment of a pre-cancerous skin lesion. Also, the present invention is directed to the use of a composition comprising glyphosate of the present invention, for the preparation of a medicament for the treatment of a pre-cancerous skin lesion.
For the purposes of the present invention, "skin cancer" refers to any type of cancer of the skin including for instance melanoma, basal cell cancer, or squamous cell cancer. A "pre-cancersus lesson" refers to a change in the skin that is not yet cancerous but may become so, including for instance an actinic keratosis. Preferably, a pre-caneous lesion is a small reddened raised area that may have a small scab, as described in the Examples.

The term "topical" and the like refers to the external surface of the skin. A composition having glyphosate is administered according to the present invention through topical application of the composition to a pre-cancerous lesion; piecing the composition in direct contact with the lesion. Topical application can include a variety of known methods, including by drop, by application via finger, or for instance a cotton pad. Preferably, the composition is applied to an abraded lesion with gentle rubbing.

The terms "treat", "treating", and "treatment", and the like, refer to ameliorating (improving or making less severe) end/or preferably to curing a pre-cancerous lesion. Said treatment may occur in a human or non-human subject having a pre-cancerous lesion. Preferably, a precancerous lesion treated according to the present invention is fully cured, and the skin healed. Treatment according to the present invention may be achieved by applying a composition of the present invention one or more times to the pre-cancerous lesion. Preferably, the composition is applied at least two, and more preferably at least three, times during a course of treatment. Also preferably, the composition is applied fewer than 20 times, more preferably fewer than 10 times, more preferably fewer than 5 times, and most preferably 3 times, 2 times, or 1 time during the treatment of a given lesion or cancer. Multiple applications are preferably spaced 3 days to 14 days apart. The composition of the present invention may be applied for instance 3 times, for instance one time every three days; or one time alone; or two times, for instance one week apart. Other treatment schedules are also contemplated with regard to this invention. While the preferred treatment is a full cure, a composition of this invention may be applied for maintenance or preventative purposes. Also, during a treatment according to the present invention, compositions having a higher concentration of glyphosate may be used to provide a leading dose and a composition having a lower glyphosate eoneotratii (preferably approximately one-half of the composition used for the loading dose) for remaining applications.

The phrase "therapeutically effective amount" refers to an amount of glyphosate [(2-phosphonomethyiamino) acetic acid] or its salts sufficient to treat (preferably cure) a pre-cancerous lesion in a subject. Preferably a single application of glyphosate to a pre-cancerous lesion will include about 1 mg to about 400 mg glyphosate; more preferably, about 4 mg to about 100 mg; more preferably, about 3 mg to about 90 mg; more preferably, about 4 mg to about 75 mg; more preferably, about 5 mg to about 30 mg; most preferably, about 5 to about 30 mg. Amounts applied to a pre-cancerous lesion may be for instance 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400 mg in a single application. The glyphosate may be present in an amount of about 2% to about 99% of the composition. The glyphosate may comprise for instance 1-5% glyphosate; 0-20% glyphosate; 11-15% glyphosate; 16-20% glyphosate; 21-25% glyphosate; 26-30% glyphosate; 31-35% glyphosate; 36-40%
glyphosate; 41-45% glyphosate; 46-50% glyphosate; Si-S5% glyphosate; 56-60% glyphosate; 61-65% glyphosate; 86-70% glyphosate; 71-75% glyphosate; 76-80% glyphosate; S1-SS% glyphosate; §5-90% glyphosate; S1-95% glyphosate; or 96-99% glyphosate; by weight, of the total composition. The glyphosate may also be present in amount of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99% by weight of the total composition. A range including the above amounts is also contemplated in the context of the present invention.

A composition of the present invention may include glyphosate alone, or with one or more active ingredients, preferably also useful in treating precancerous lesions, and/or one or more inactive ingredients, for instance to provide effective delivery of the glyphosate. Such inactive ingredients include for instance water and minor formulating ingredients, as well as other compounds suitable for topical application. Preferably, the glyphosate is in the form of an isopropylamine salt. The composition may be a liquid solution, gel, cream, ointment, or other form suitable for topical application to the skin. Preferably, the composition is in aqueous solution, more preferably the composition has an acidic pH, even more preferably a pH in the range of about 3.5 to about 6, and more preferably, a pH in the range of 4.5.

The composition employed in the following examples are products identified in EPA Reg No. 71995-29, (Roundup Weed & Grass Killer Concentrated Plus) EPA Reg No. 71995-27 and/or EPA Reg No. 71995-27-239 (Ortho Basic Solutions Weed & grass Killer Ready-to-Use, spray bottle, 1.92% glyphosate (Ortho composition)). The MSDS for these products are included herewith and incorporated by reference as needed to aid in describing compositions that may be used in the present invention.

The following examples are intended to exemplify the present invention, but not to be limiting. The inspiration for the invention came from the inventor mentally connecting the concept of the spread of plant spores to metastasis in the human body.

EXAMPLE 1

A pre-cancerous lesion (actinic keratosis) on an elderly man’s face was treated with a glyphosate composition. The lesion was small, approximately 1 mm in size and located 20 mm to the left of the lower edge of the man’s left nostril. The lesion persisted for approximately 8 months prior to treatment according to the present invention, resisting three attempts at treatment with alcohol and/or topical antibiotics, such that the lesion would redden slightly and trickle blood, but not heal

A small scab covered the lesion prior to treatment according to the present invention. The scab, lesion, and area surrounding the lesion were gently cleansed with Dial liquid soap and the scab removed, to provide maximum exposure of the lesion to the glyphosate.

A small amount of Ortho composition (Ortho Basic Solutions Weed & Grass Killer Ready-to-Use composition, in an original spray bottle, having 1.92% glyphosate isopropylamine salt), was sprayed
into the palm of the subject's hand and the cotton pad at the end of a Q-tip immersed in the Ortho
composition. When the Q-tip was saturated with the Ortho composition, the saturated end of the Q-tip
was gently but firmly pushed into the lesion. The Q-tip was twisted slightly to ensure maximum
coverage and removed. This process was repeated. There was a slight stinging as the Ortho
composition contacted the tissue. No other side effects were noted. The area was washed again
orally the next morning. No other substances were applied to the lesion.

The lesion and surrounding area was observed daily, several times during the day, to follow the
progression of the treated area. The redness began disappearing, and after four days, the skin was
similar to surrounding tissue, although still with a slight difference. The area was slightly reddish,
blotchy, and there was a tiny crater where the lesion had been but appeared to be healing, no rawness,
no scabbing, and the skin appeared normal. The small lesson was treated and fully healed in 7 days, with
just one application of the Ortho composition.

A second lesion (actinic keratosis! on the same male subject was on the left side of the subject's throat,
about 50mm directly below the subject's left ear. The lesion would not heal. It would scab over for 3 to
4 days, and then the scab would leave, revealing the reddened unhealed area underneath. The lesion
was covered with antibiotics several times, causing it to scab and eventually slough off, again revealing a
reddenened unhealed area. The lesion was sensitive when touched; care was taken during shaving to
avoid pain and worsening of the lesion. This continued for 6-8 months.

The second lesion was treated with the Ortho composition. The lesion was thoroughly cleansed with
Dial liquid soap to expose as much of the lesion as possible. Most of the lesion became exposed as the
scab was gently removed. After cleaning, the lesion showed a raw, unhealed area with a crater-like
appearance in the upper end of the unhealed area. The lesson was not rubbed vigorously, but was
rubbed firmly, to expose as much lesion tissue as possible. The lesion was about 15mm long and gmm
wide, running diagonally upward toward the left ear, with the top of the lesion about 50mm below the
lobe of the left ear.

The Ortho composition was squirted into the subject's hand and end of Q-tip was immersed into
the liquid, generally as discussed regarding the first lesion above. After gently squeezing the excess fluid
from the Q-tip, the Ortho composition was topically applied to the lesion, so that the entire lesion was
covered, with attempts to not extend application much over the borders of the lesion.

The next day the entire lesion was covered with a scab. The area was not further treated with the Ortho
composition. The area was washed gently with Dial liquid soap and water; care was takeo to not irritate
the area when the subject shaved.

There was a slight stinging sensation when the Ortho composition was applied, similar to the above
discussion of the first lesion. The sensation quickly passed and did not continue or repeat. Another
similarity between treatment of the two lesions is that soon after application, the area felt better. There
was a reduced sensation of discomfort. The lesion was observed daily for progress. The area was quiet,
no discharge, and slightly less redness.
Four days later the scab appeared to slough off on its lower edge. In the following days, this gradually moved upward. The area was less sensitive to pain but would still produce a pain sensation when rubbed or touched with a razor.

As the scab area sloughed off, the area under it was somewhat reddened but the tissue appeared healed. There was no rawness and the tissue appeared similar to the tissue adjoining it. This redness gradually lessened as time progressed.

Eighteen days later there was only a small round, unhealed area, the size of a BB, that had not completely healed. It was in the area where there appeared to be a crater like formation at the upper end of the lesion. Five days later, the entire area was healed.

Only one application of the Ortho composition was made to the lesion,

EXAMPLE II

The Ortho composition was directly and topically applied by gentle rubbing to a precancerous skin lesion (actinic keratosis) on the face of a human male subject. Just below his eye. Prior to treatment, the lesion was treated in a manner described in Example I. It is estimated that approximately 5 mg of glyphosate was applied to the lesion. The lesion was approximately 8 mm wide and 3 mm long, mildly raised and somewhat painful to the touch, with a scaly, reddened appearance and a small area of broken skin with a small scab on it. The amount of composition applied was sufficient to cover and coat the lesion. The application was applied arsd, over the spare of 2 days, the scab disappeared and redness and swelling lessened. No adverse effects were reported by the subject.

EXAMPLE III

The Ortho composition of Example II was applied to a different lesion (actinic keratosis) on the same subject, having similar characteristics to that described in Example II. Application occurred 3 times; Day 0, Day 3, and Day 7. It is estimated that each application included approximately 6.0 mg of glyphosate. The scab disappeared and redness and swelling lessened and then disappeared over the size of the following 3 weeks. No adverse effects were reported by the subject.

EXAMPLE IV

A composition (EPA Reg. No. 1995-29) having approximately 18% of isopropylamine salt of glyphosate in an aqueous solution, pH about 5, was directly applied by gentle rubbing to a precancerous skin lesion (actinic keratosis) on the tip of the ear of a human male subject. The lesion was small (about 3 mm long and 2 mm wide) and scabbed, and was abraded prior to application of the composition to allow the composition direct access to the raw skin under the scab. A blood blister appeared over the lesion and was punctured and drained during treatment. The composition was reapplied 4 days after the initial application, with any scab again abraded. The lesion was completely healed within 10 days. Other than the formation of the blood blister, no adverse effects were reported by the subject.
APPENDIX

Material Safety Data Sheet (MSDS), SPA Reg Ho, 71995-27-239 (Ortho Baste Solutions Weed & Grass Killer Ready-to-Use)

Safety Data Sheet, EPA Reg No. 71956-29 (Roundup Weed & Grass Killer Concentrate Plus)
MATERIAL SAFETY DATA SHEET

1. PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME: ORTHO® Basics Solutions™ Weed & Grass Killer Ready-To-Use
PRODUCT DESCRIPTION: Herbicide

MANUFACTURER:
ORTHO BASICS SOLUTIONS
1100 GLENSIDE AVENUE
VILLAGER, PA 19085

24 HR. EMERGENCY TELEPHONE NUMBERS

VILLAGER, PA: (800) 424-5120
Emergency Physician: 1-800-528-8600

2. COMPOSITION / INFORMATION ON INGREDIENTS

Chemical Name

Glyphosate, isopropylamine salt

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW
IMMEDIATE CONCERNS: CAUTION. CAUSTIC. IRITATION. AVOID CONTACT WITH EYES OR CLOTHING. WASH THOROUGHLY WITH SOAP AND WATER. AVOID HANDLING KET OUT OF REACH OF CHILDREN.

WARNING:
YES: Moderately irritating to the skin.
SKIN: Not expected to cause skin irritation.

4. FIRST AID MEASURES

EYES: Flush eyes immediately with plenty of water for at least 15 minutes. Use a constant stream of water. If irritation persists, call a doctor.
SKIN: Wash off immediately with soap and water. If irritation persists, call a doctor.
INHALATION: If exposed to smoke, call a poison control center for emergency assistance.

ANTIDOTES: Treatment with atropine and oximes is not indicated.
NOT TO PHYSICIAN: This product is not an inhibitor of cholinesterase.

COMMERCIAL PRODUCT LABEL: For commercial use only. The above measures are the most conservative. Pesticide Registration (FIR) Notice 2001-1, January 2, 2001, and would apply in the event a product label is not immediately available.

5. FIRE FIGHTING MEASURES
FLASHPOINT: Method: Direct heat
EXTINGUISHING MEDIA: Dry chemical, water
HAZARDOUS COMBUSTION PRODUCTS: CO, phosphorus (phosgene)
EXPLOSIVE HAZARDS: No known
FIRE FIGHTING PROPERTIES: Self-contained breathing apparatus. Equipment should be thoroughly decontaminated after use.

6. ACCIDENTAL RELEASE MEASURES
SMALL SPILL: Sweep up spills. Use good housekeeping practices. Avoid contact with clothing, skin, and eyes. Wash hands after handling.
LARGE SPILL: Minimize spread. Keep out of drains, sewers, ditches, out of waste ways.

7. HANDLING AND STORAGE
HANDLING: Wear rubber or neoprene gloves. Wash thoroughly after handling. Avoid contact with eyes, mouth, and skin. When handled, equipment should be kept out of reach of children. Wash hands and contaminated skin thoroughly after handling.
STORAGE: Store in original container under appropriate conditions. Use only in original container. Follow label storage recommendations.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION
ENGINEERING CONTROLS: No special ventilation is necessary.
PERSONAL PROTECTION: CLOTHING, FACE: For application in any product in any section, use appropriate personal protective equipment. Eye protection is needed. where there is a significant potential for eye contact. Wear chemical resistant and high visible glasses.
SKIN: Although this product does not present a significant skin contact, minimize skin contact by following good industrial practice. Wearing protective gloves is recommended. Wash hands and contaminated skin thoroughly after handling.
RESPIRATORY: Avoid breathing vapor or mist.

9. PHYSICAL AND CHEMICAL PROPERTIES
PHYSICAL STATE: Liquid
ODOR: Slight or r.
APPEARANCE: Clear
PHT; 4.0 to 7.0
SOLUBILITY IN WATER: Miscible with water
SPECIFIC GRAVITY: 1.01 Water = 1.00 at 20°C

10. STABILITY AND REACTIVITY

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8
STABILITY:

HAZARD N POLYMORPHIZATION: NO

INCOMPATIBILITY: Material reacts with galvanized steel or unlined milled steel to produce hydrogen gas.

11. TOXICOLOGICAL INFORMATION

ACUTE

IV/KI: Rabbit - moderately irritating (testing: repeated irritation test: subcutaneous 100 mg/kg 1 time, 7 EPA IHRA irritation category III).

DEMONSTRATIVE STUDY: Occluded (OA) 11 1/2 mg/m² 6 hr. / 8% - pH: EPA IHRA irritancy category V. (in: Natarajan, 1. 2. 3. (Rahman, 1981) IHRA irritancy category IV.)

ORAL, LD₅₀ Rat: 240 mg/kg, pH: IHRA irritancy category IV.

INHALATION: LC₅₀ (4 hr) 10 mg/L, pH: IHRA irritancy category IV.

SKIN: 1 mg/cm² Single application in rabbits. Primary 1 mg/cm²: index 1-3.

ENVIRONMENT: NO: Caution: pig, swine: cause allergic skin reaction.

GLYPHOSATE: In vitro: Phosphate-buffered saline absorption studies were conducted with a film, base, comprised of 82% w/w hydrolyzing salt of glyphosate (MÖHLE 1998) subcutaneous 3 X daily. Applied daily for 3 days resulted in slight skin irritation. Flap. 6-month feeding study: Only slight body weight changes noted. 90 day oral: no visible chronic oral effect. 90 day feeding: Slight weight gain at the high dose level group animals.

MUTAGENICITY: NO: Glyphosate is not considered to be a mutagen. Glyphosate did not produce mutations in any of the long-term mutagenicity studies. EPA has classified glyphosate in category 1A (insufficient evidence of nonmutagenicity for humans). A 2-year feeding study: Reduced body weight gain and effects on liver weights were observed at high dose levels. Rats, 2 year feeding study. Reduced body weight gain and effects observed at the high dose level in one study, while no treatment related effects observed in a second study conducted at lower dose levels. Flap: No adverse effects observed in feeding studies with rats.

11. GENOTOGENICITY: Glyphosate: No evidence of genotoxic effects. Results of in vivo and in vitro genotoxicity studies indicate that no mutagenic effects were noted. This included dose levels of glyphosate that were materially toxic.


MI TABIL: NO: Glyphosate: Glyphosate is not phototoxic in various phototaxonomic tests involving animals and microbial bacterial cells.

V. ECOLOGICAL INFORMATION

ECOTOXIC OR ECOLOGICAL INFORMATION: Available data for a similar formulation are summarized below: Aquatic, fish conditions: 48-hr: 1,500 mg/L very toxic 1,000 mg/L: Very toxic; 72-hr: 1,500 mg/L very toxic 1,000 mg/L: Very toxic; 96-hr: 1,500 mg/L very toxic 1,000 mg/L: Very toxic; 144-hr: 1,500 mg/L very toxic 1,000 mg/L: Very toxic; Fish, freshwater algae species: NO ATM 24-hr: 30 mg/L very toxic 3 mg/L: Toxic; NO ATM reproduction: 100 mg/L body e. coli. Large organs: Flap extract - no effect. Flap: no effect.

The results of degradation and biodegradation studies with the active ingredient indicate that this product would be practically nonpersistent to aquatic species and highly toxic. The results of biodegradation studies with the active ingredient indicate that this product would be rapidly adsorbed to soil, readily biodegradable in soil and water, and does not bioaccumulate.

33. DISPOSAL CONSIDERATIONS

PROHIBIT: Insignia: Not to product, label, test, dispose, or use in any manner, whether as solutions, emulsions, or mixtures. Place empty containers in trash. Do not pour down any drain.

14. TRANSPORT INFORMATION

file://C:\TEAM\PRIVATE\ Pest%20Registration%20MSDS%20Ortho%20Basic%20Eng... 4/2/2004
Basic Solutions® Weed & Grass Killer Ready-To-Use

DOT (DEPARTMENT OF TRANSPORTATION)
PROPER SHIP. NAME: Not DOT regulated

SPAS 1A1: SHIP. NOTES. The carrier should not apply to all shipping along a route or the specific transport, or appropriate, dangerous goods regulations, or additional or different shipment requirements (e.g., transportation and markings) or any specific safety requirements.

UNITED STATES
TSCA TOXIC SUBSTANCE CONTROL ACT

TSCA REA V. MURPHY: All as a FELINA resulted components are in the US TSCA Inventory -

6.0 TASTER INFORMATION

NFPA CODES
FIRE: 0 HEALTH: 1 REACTIVITY: 0

ADDITIONAL HAZARDOUS INFORMATION: NFPA Hazards Ratings: 0 Health, 1 Reactivity, 2 Flammability, 3 High. 

GENERAL STATEMENTS: This document contains health, safety, and environmental information useful to emergency response agencies, health care providers, manufacturers, and workers. It does not replace the precautionary language and instructions or the storage and disposal information found on the product label.

COMMUNICATE: Use of this product is regulated by the U.S. Environmental Protection Agency (EPA) through the approval product label. It is a violation of Federal law to use this product in a manner inconsistent with its labeling.

MANUFACTURER DISCLAIMER: The information contained herein is, to the best of the manufacturer's (see Section 1) knowledge and belief, accurate and reliable as of the date of preparation of this document. However, no warranty or guarantee, express or implied, is made as to the accuracy or reliability, and the manufacturer shall not be liable for any loss or damage arising out of the use thereof. No authorization is given or implied to use any patented invention without license. In addition, the manufacturer shall not be liable for any injury resulting from abnormal use from any failure to adhere to recommended practices or from any hazards inherent in the nature of the product.

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1. PRODUCT AND COMPANY IDENTIFICATION

Product name
Rainilip® Wee J & Grass Killer Concentrate Plus

EPA Reg. No.
71995-26

Chemical name

Not applicable

Suppliers
None.

Company
Monson & Company, Lawn & Garden Products, P.O. Box 418, Marysville, OH 43041

Telephone: 1-800-216-7219

E-mail: TS-SAFETY@DATASHEET@DOMINO.COM

Emergency numbers
FOR CHEMICAL EMERGENCY, SPILL LEAK, FIRE, EXPOSURE, OR ACCIDENT Call CHEMTRI¢ - Day or Night. 1-800-424-9399 toll free in the continental U.S., Puerto Rico, Canada, or Virgin Islands. For calls originating elsewhere: 703-227-3887 (collect calls accepted).

FOR MEDICAL EMERGENCY - Day or Night: 1-866-246-7219

2. HAZARDS IDENTIFICATION

Emergency exposure

Appearance and odour (colour/taste/odour): Amber / Liquid / Musk

CAUTION:
CAUSES MODERATE EYE IRRITATION

Potential health effects

Likely routes of exposure
Skin contact, eye contact, inhalation

Eye contact, short term
May cause temporary eye irritation.

Skin contact, short term
Not expected to produce significant adverse effects when recommended use instructions are followed.

Inhalation, short term
Not expected to produce significant adverse effects when recommended use instructions are followed.

Refer to section 16 of the I.C. and section 12 of the environmental impact statement.

OSHA St.uss
This product is hazardous according to the OSHA Hazard Communication Standard - 29 CFR 1910.1200.

3. COMPOSITION/INFORMATION ON INGREDIENTS

Activ® Ingredients

Isopropylamine salt of N-(phosphonomethyl)glycine; Isopropylamine salt of glycine, 
\(\alpha,\beta\)-Dihydroxypropyldi(\(\alpha\),\(\beta\)\)-pyrazinyl-di bromide; (Diquat dibromide)
Composition

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>CAS No.</th>
<th>% by weight (approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron(II) nitrate salt of glyphosate</td>
<td>78541-94-0</td>
<td>18</td>
</tr>
<tr>
<td>Disodium ethylenediamine tetrahydrogen diphosphate</td>
<td>62-00-7</td>
<td>0.73</td>
</tr>
<tr>
<td>Water and minor formulation ingredients</td>
<td></td>
<td>81.27</td>
</tr>
</tbody>
</table>

The specific chemical identity is being withheld because it is trade secret information of Monsanto Company.

4. FIRST AID MEASURES

Use personal protection recommended in section 8.

Eye contact
If in eyes, hold eye open and rinse slowly and gently for 15-20 minutes. Remove contact lens if present, after first 5 minutes, then continue rinsing.

Skin contact
Wash affected skin with plenty of water.
Wear resistant gloves and protective clothing, protective gloves and protective eyewear. Wash clothes and gloves before re-use.

Inhalation
Remove to fresh air.

Advice to doctors
This product is not intended for medical treatment.

Antidote
Treatment with atropine and other anticholinergic drugs is not indicated.

5. FIGHTING FIRE MEASURES

Flash point
Does not flash.

Extinguishing media
Recommended: Water, dry chemical, CO2.

Unusual fire and explosion hazards
None.

Environmental precautions: See section 11.

11.3.2.1, 3.4.1.2, 3.4.1.3.1.

Firefighting equipment
Self-contained breathing apparatus.

Equipment should be thoroughly decontaminated after use.

6. ACCIDENTAL RELEASE MEASURES

Personal precautions
Use personal protection recommended in section 8.

Environmental precautions
SMALL QUANTITIES:
Low environmental hazard.

LARGE QUANTITIES:
Minimize spread.
Keep out of de ins, sewers, drains and water ways.

Methods for cleaning up -
SMALL QUANTITIES.
Flush spill with water.
LARGE QUANTITIES:
As soon as possible, place absorbing material.
Dig up heavily contaminated soil.
Collect in a suitable container for disposal.

Refer to section 6 for types of container.

Plunge residues - i.e. spill quantities of water
Minimize use of water to prevent waste disposal problems.

Refer to section 6 for disposal of spilled material.

Use handling recommendations in Section 7 and personal protection recommendations in Section 6.

7. HANDLING AND STORAGE

Good industrial practice in housekeeping and personal hygiene should be followed.

Handling
Avoid contact with eyes. When using do not eat, drink or smoke.
Wash hands thoroughly after handling or contact.
Do not contaminate drains, sewers and waterways when disposing of equipment and waste oil.
Empty packages remain exposed residue and dust.
Observe all labelled safeguards until container is cleaned, reconditioned or destroyed.

Storage
Compatible materials for storage: stainless steel, aluminium, fibreglass, plastic, glass lining.
Incompatible materials for storage: galvanized steel, unlined mild steel. See section 6.

Keep out of reach of children.

Keep away from food, drink and animal feed.

Keep only in the original container.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Airborne exposure limits

<table>
<thead>
<tr>
<th>Component</th>
<th>Exposure Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isopropylamine salt of glyphosate</td>
<td>No specific occupational exposure limit has been established.</td>
</tr>
<tr>
<td>Diquat dibromide</td>
<td>TLV (ACGIH): 9.5 mg/m³; inhalable fraction: 50%, No specific occupational exposure limit has been established. The exposure limit indicated is for the inhalable fraction.</td>
</tr>
<tr>
<td></td>
<td>TLV (ACGIH): 8.1 mg/m³: respirable fraction, skin. No specific occupational exposure limit has been established. The exposure limit indicated is for the inhalable fraction.</td>
</tr>
</tbody>
</table>

No specific occupational exposure limit has been established.

Engineering controls

No specific occupational exposure limit has been established.
Provide adequate ventilation to keep airborne concentrations below exposure limits.

Eye protection
If there is significant potential for contact:
Wear chemical goggles.

Skin protection
No special requirement when used as recommended.
If repeated or prolonged contact:
Wear chemical resistant gloves.

Respiratory protection
If airborne exposure is excessive:
Wear respirator.
Full facepiece/nose/helmet respirator replaces to red on chemical goggles

When recommended, consult regulatory specific, eg. local, for appropriate type of equipment.

9. PHYSICAL AND CHEMICAL PROPERTIES

These physical data are typical values on material tested but may vary from sample to sample. Typical values should not be construed as a guaranteed absolute property for specific use or specifications for the product.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour/colour range</td>
<td>Amber</td>
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<tr>
<td>Odour</td>
<td>Musk</td>
</tr>
<tr>
<td>Form</td>
<td>Liquid</td>
</tr>
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<td>Physical form changes (melting, boiling, etc.)</td>
<td></td>
</tr>
<tr>
<td>Melting point</td>
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</tr>
<tr>
<td>Boiling point</td>
<td>No data</td>
</tr>
<tr>
<td>Flash point</td>
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</tr>
<tr>
<td>Explosive properties</td>
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</tr>
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<td>Specific gravity</td>
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<td>No significant volatility; aqueous solution</td>
</tr>
<tr>
<td>Vapour density</td>
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</tr>
<tr>
<td>Evaporation rate</td>
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</tr>
<tr>
<td>Density</td>
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</tr>
<tr>
<td>pH</td>
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</tr>
<tr>
<td>Partition coefficients [log P]</td>
<td>log P &gt; -4.2 at 24°C (alkylphosphate)</td>
</tr>
<tr>
<td>Partition coefficients [log K]</td>
<td>log K &gt; -4.60 at 20°C (alkyl diethers)</td>
</tr>
</tbody>
</table>

10. STABILITY AND REACTIVITY

Stability
Stable under normal conditions of handling and storage.

Oxidising properties
No data.
Monsanto Company, ism & Garden Products
Roundup Products, Weed & Grass Killer Concentrate Plus

Materials to avoid/Reactivity
Reacts with galvanized steel or unlined mild steel to produce hydrocyanic acid, a highly flammable gas that could explode.

Hazardous decomposition
Thermal decomposition: Hazardous products of combustion: see section 5.

Self-accelerating decomposition temperature (SADT)
No data.

11. TOXICOLOGICAL INFORMATION
This section is intended for use by toxicology experts and other health professionals.

Monsanto has not conducted toxicity studies on this product. Data obtained on similar products and on components are summarized below.

Similar formulation

Acute oral toxicity
Rat, LD50: > 5,000 mg/kg body weight
Practically non-toxic.
FFR A category IV.

Acute dermal toxicity
Hare, LD50: > 5,000 mg/kg body weight
Practically non-toxic.
FFR A category IV.

Skin irritation
Rabbit: 3 animals, OECD 404 test:
Days to heal: 2
Primary irritation index (PII): 8.4 3.0
Legitimately non-irritating.
FFR A category IV.

Eye irritation
Rabbit, 3 animals, OIEX 13 135 seal:
5 s to heal: 3
FFR A category III.
Moderate irritation.

Acute inhalation toxicity
Rat, LC50, 4 hours, animal: 1
Practically non-toxic.
FFR A category IV.
No 4-hr LC50 is the maximum tested concentration.

Skin sensitization
Guinea pig, 3-induction Draize test:
Positive incidence: 0 %

 NSS mice

Mutagenicity
In vitro and in vivo mutagenicity test:
Not mutagenic.

Reproductive toxicity
Rabbit, dermal: 21 days;
NOAEL toxicity: > 5,000 mg/kg body weight.
Target organs/systems: none.
Other effects: none
Rat, oral, 3 months:
NOAEL toxicity: > 20,500 mg/kg diet
Target organ/systems: none
Other effects: none

Chronic effects/teratogenicity
Mouse, oral, 24 months:
NOAEL toxicity: 5,000 mg/kg diet
Target organ/system: liver
Other effects: decreased body weight gain, histopathologic effects
NOAEL tumour: > 30,000 mg/kg diet
Tumours: none
Rat, oral, 24 months:
NOAEL toxicity: 8,000 mg/kg diet
Target organ/system: testes
Other effects: decrease of body weight gain, histopathologic effects
NOAEL tumour: > 30,000 mg/kg diet
Tumours: none

Toxicity to reproduction/fertility
Rat, oral, 2 generations:
NOAEL toxicity: 10,000 mg/kg diet
PREREL reproduction: 30,000 mg/kg diet
Target organ/systems in parents: none
Other effects in parents: decrease of body weight gain
Target organ/systems in pups: none
Other effects in pups: decrease of body weight gain
Effects on offspring only observed with maternal toxicity.

Developmental teratogenicity
Rat, oral, 6 - 19 days of gestation:
NOAEL toxicity: 1,000 mg/kg body weight
NOAEL development: 1,000 mg/kg body weight
Other effects in mother: minimal decrease of body weight gain, decrease of survival
Developmental effects: weight loss, post-implantation loss, delayed ossification
Effects on offspring only observed with maternal toxicity.
Rabbit, oral, 6 - 27 days of gestation:
NOAEL toxicity: 175 mg/kg body weight
NOAEL development: 175 mg/kg body weight
Target organ/systems in mother animal: none
Other effects in mother: minimal decrease of survival
Developmental effects: none

Irritant/lachrymatory
Mutagenicity
In vitro and in vivo mutagenicity test(s):
Equivalent response.

Repeated dose toxicity:
Rat, inhalation, 3 weeks:
NOAEL toxicity: 0.1 mg/m3
Target organ/systems: lung
Other effects: organ weight change, histopathologic effects, inflammation

Chronic effects/teratogenicity:
Dog, oral, 52 weeks:
NOAEL toxicity: 0.5 mg/kg body weight day
Target organ/systems: eyes, adrenals
Other effects: organ weight change
Rat, oral, 21 days:

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NOEL toxicity: 0.58 mg/kg body weight/day
Target organs/systems: eyes
NOEL tumour: 2.91 mg/kg body weight/day
Tumours: bone marrow, (sarcoma)
Tumours not related to treatment.
Mouse, oral, 2 years:
NOEL toxicity: 3.56 mg/kg body weight/day
Target organs/systems: kidney
Other effects: decrease of body weight gain, organ weight change
NOEL tumour: > 27.6 mg/kg body weight/day
Tumours: none

Toxicity to reproduction/fertility:
Rat, oral, 2 generations:
NOEL toxicity: 0.8 mg/kg body weight/day
NOEL reproduction: 4 mg/kg body weight/day
Target organs/systems in parents: eyes
Other effects in parents: decrease of body weight gain, decrease of food consumption
Other effects in pups: decrease of body weight gain, decrease of litter survival
Effect on offspring only observed with maternal toxicity

Developmental toxicity/neonatal studies:
Rat, oral, 7 - 16 days of gestation:
NOEL toxicity: < 4 mg/kg body weight/day
NOEL development: 12 mg/kg body weight/day
Other effects in mother animal: decrease of body weight gain, decrease of food consumption
Developmental effects: weight loss, skeletal variations, visceral malformations, delayed ossification
Effect on offspring only observed with maternal toxicity.
Rabbit, oral, 7 - 19 days of gestation:
NOEL toxicity: 1 mg/kg body weight/day
NOEL development: 1 mg/kg body weight/day
Other effects in mother animal: decrease of body weight gain, decrease of food consumption
Developmental effects: visceral variations, delayed ossification
Effect on offspring only observed with maternal toxicity.
Mouse, oral, 6 - 15 days of gestation:
NOEL toxicity: 1 mg/kg body weight/day
NOEL development: 2 mg/kg body weight/day
Other effects in mother animal: decrease of body weight gain, breathing irregularities, neurotoxic signs, decrease of survival
Developmental effects: weight loss, skeletal variations
Effect on offspring only observed with maternal toxicity.

Acute neurotoxicity:
Rat, oral, single dose, gavage:
NOEL: 25 mg/kg body weight
Other effects: neurovascular effects
Not neurotoxic.

Reproductive neurotoxicity:
Rat, oral, 14 weeks, dietary:
NOEL: 8 mg/kg body weight/day
Target organs/systems: eyes
Other effects: decrease of body weight gain
Not neurotoxic.

12. ECOLOGICAL INFORMATION

This section is intended for ecotoxicologists and other environmental specialists.

Data obtained on a more concentrated glyphosate formulation and/or glyphosate are summarized below. The minor active ingredient tri is not predicted to significantly contribute to the ecotoxicity of this formulation.
Similar glyphosate formulation

Aquatic toxicity, fish
Rainbow trout (Oncorhynchus mykiss):
Acute toxicity, 96 hour LC50: 5.5 mg/L
Moderately toxic.
Blugill sunfish (Lepomis macrochirus):
Acute toxicity, 96 hour LC50: 7.3 mg/L
Exremely toxic.

Aquatic toxicity, invertebrates
Water flea (Daphnia magna):
Acute toxicity, 48 hours static, EC50: 11 mg/L
Slightly toxic.

Aqual toxicity
Male fat duck (Anas platyrhynchos):
Dietary toxicity, 5 days: LC50: > 520 mg/kg diet
Practically non-toxic.
Belsonite quail (Coturnix virgo):
Dietary toxicity, 5 days: LC50: > 5620 mg/kg diet
Practically non-toxic.

Arthropod toxicity
He = 3% beer (Apis mellifera):
Oral contact, 48 hours, LD50: > 100 µg/bee
Practically non-toxic.

Soil artemisin toxicity, in ericaceous plants
Earthworms (Eisenia fetida):
Acute toxicity, 14 days, LC50: > 1,250 mg/kg soil
Practically non-toxic.

Isopropylamine salt of glyphosate (625g)

Aquatic toxicity, algae/aquatic plants
Green algae (Secrondemia subplacata):
Acute toxicity, 72 hours, static, EC50 (biomass): 72.9 mg/L
Slightly toxic.

N-(phosphonomethyl)glycine (glycine amide)

Bioaccumulation
Blugill sunfish (Lepomis macrochirus):
Whole fish: BCF: < 1
No significant bioaccumulation is expected.

Disposal
Salt, field:
Half life: 3 - 174 days
Koc: 550 - 60,000 L/kg
Adsorbs well to soil.
Water, aerated:
Half life: 6 - 17 days

13. DISPOSAL CONSIDERATIONS

Product
Keep out of sewers, ditches, and waterways.
Recycle if appropriate facilities and equipment available.
Dispose of as hazardous industrial waste.
Follow all local/regiona/l/national/international regulations.

Container
See the individual container label for disposal information.
Empty packages retain product residue and dust.

G-ters all lab-leS safeguards until container is cleaned, neutralized and decontaminated.

Empty packaging completely.

Do NOT contaminate water when disposing of these wastes.
Ensure packages cannot be opened.

Do NOT fill container.

Store for sale in the approved waste disposal service.

Recover if appropriate facilities/equipment available.
Follow all local/regiona/l/national/international regulations.

14. TRANSPORT INFORMATION

"- data provided is with consent from the information only. Please apply the applicable regulations properly.

Not hazardous under the applicable DOT, ICAO/ADR, IMDG and Mexican regulations.

15. REGULATORY INFORMATION

TSCA Inventory
Exempt

GHS Hazardous Components

S as faCt

SARA Title III Rules
Section 311/312 Hazard Categories:
Immediate
Section 302 Extremely Haz. Substances
Section 313 Toxic Chemicals
Not applicable.

CERCLA Reportable Quantity
Not applicable.

16. OTHER INFORMATION

The information given here is not necessarily exhaustive but is representative of relevant, reliable data.
Follow all local/regiona/l/national/international regulations.

Please consult suppliers if further information is needed.

This Safety Data Sheet has been prepared following the EU Directive 91/155/EEC as last amended by EU Directives 2001/58/EC and according to EU Regulation 1907/2006.

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Monsanto Company, Lawn & Garden Products

Full denaturation of most frequently used enzymes, SBI (Bacteria, Streptomyces, Proteus, PDB (Bacterial Protease) Lemon, O157 and

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MONSANTO Company, Lawn & Garden Products

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CLAIMS

1. A method of treating a pre-cancerous lesion of the skin, comprising the step of topically applying a composition having glyphosate to the lesion in a therapeutically effective amount.

2. The method of claim 1, wherein the glyphosate is in the form of an isopropylamine salt.

3. The method of claim 1, wherein the glyphosate comprises about 1% to about 99% by weight of the composition.

4. The method of claim 1, wherein the glyphosate comprises about 2% to about 20% by weight of the composition.

5. The method of claim 1, wherein the composition has a pH of about 3.5 to about 6.

6. The method of claim 1, wherein about 10 to about 100 mg of glyphosate is applied to a lesion in at least one application.

7. The method of claim 1, wherein about 50 to about 70 mg of glyphosate is applied to a lesion at least one application.

8. The method of claim 1, wherein the composition is applied to a lesion at least twice over a period of from 3 to 7 days.

9. The method of claim 6, wherein the composition is applied to a lesion at least twice over a period of from 3 to 7 days.

10. The method of claim 1, wherein the composition is the subject of EPA Reg. No. 71995-27.

11. The method of claim 1, wherein the composition is the subject of EPA Reg. No. 71995-29.

12. The method of claim 1, wherein the composition is the subject of EPA Reg. No. 71995-27-239.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 17/02 (2016.01)
CPC - A61Q 19/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61P 17/02 (2016.01);
CPC: A61Q 19/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data) EBSCO; IEEE.com; Google Scholar, Google Patent; lesion, tumor, cancer, skin, topical, glyphosate, isopropylamine, phosphonometilamino, roundup, ortho weed, therapeutic, treatment, dosage, mg

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>Y</td>
<td>US 2010/0247463 A1 (YU, KJ et al.) 30 September 2010; paragraphs [0003]-[0004], [0007], [0027], [0068], [0078], [0083], [0088]</td>
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<td>Y</td>
<td>US 6,509,325 B1 (NOSANCHUK, JD et al.) 21 January 2003; column 4, lines 13-28</td>
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<td>US 2004/0077608 A1 (ABRAHAM, W) 22 April 2004; paragraphs [0012], [0050], [0054], [0067]</td>
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<td>A</td>
<td>KR 2013/0119912 A (GTX INC) 01 November 2013; see translation; entire document</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search
07 January 2016 (07.01.2016)

Date of mailing of the international search report
09 FEB 2016

Name and mailing address of the ISA/
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer
Shane Thomas
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PCT DSB: 571-272-7774

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