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

OFFICE OF
PREVENTION, PESTICIDES
AND
TOXIC SUBSTANCES

22/OCT/2002

MEMORANDUM

Subject:	Name of Pesticide Product:	MON 78481 Herbicide
	EPA File Symbol:	524-LUG
	DP Barcode:	D284522
	Case No:	072404
	PC Code:	103613, 128712
From:	Eugenia McAndrew, Biologist Technical Review Branch Registration Division (7505C)	EM SCR
To:	Vickie Walters, PM Team 25 Herbicide Branch Registration Division (7505C)	
Applicant:	Monsanto Company 600 13th Street N.W., Suite 660 Washington, D.C. 20005	

FORMULATION FROM LABEL:

	Active Ingredient(s):		% by wt.
103613	Glyphosate in the form of its potassium salt	44.76	
128712	Carfentrazone-ethyl		0.19
	Inert Ingredient(s):		55.05
		Total:	100.00%

ACTION REQUESTED: PM requests review of acute toxicity data for MON 78481 Herbicide, EPA File Symbol 524-LUG.

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BACKGROUND: Monsanto Company has submitted six acute toxicity studies in support of registration of MON 78481 Herbicide, EPA File Symbol 524-LUG, a new end-use product containing glyphosate and carfentrazone-ethyl as the active ingredients. The studies were assigned MRID numbers 457053-02 to -07. The studies were conducted at Springborn Laboratories, Inc., Spencerville, Ohio.

RECOMMENDATIONS: The six studies have been reviewed and are classified as acceptable.

The acute toxicity profile for MON 78481 Herbicide, EPA File Symbol 524-LUG, is as follows:

acute oral toxicity	IV	Acceptable	MRID 45705302
acute dermal toxicity	IV	Acceptable	MRID 45705303
acute inhalation toxicity	IV	Acceptable	MRID 45705304
primary eye irritation	I	Acceptable	MRID 45705305
primary skin irritation	III	Acceptable	MRID 45705306
dermal sensitization	Negative	Acceptable	MRID 45705307

LABELING: Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System.

PRODUCT ID #: 000524-00543

PRODUCT NAME: MON 78481 Herbicide

PRECAUTIONARY STATEMENTS

Hazards to Humans and Domestic Animals:

SIGNAL WORD: DANGER

SPANISH SIGNAL WORD: PELIGRO
Si usted no entiende la etiqueta, busque a alguien para que se la explique a usted en detalle.
(If you do not understand the label, find someone to explain it to you in detail.)

Contains Petroleum Distillate.

Restricted Use Pesticide due to toxicity categories. For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification. PM does not need required restricted use because of eye irritation.

Corrosive. Causes irreversible eye damage. Avoid contact with skin or clothing. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). Wear long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves (such as Barrier Laminate, Butyl Rubber, Nitrile Rubber, Viton, Barrier Laminate, Viton, Selection Category F, G). If the Selection Category F, G gloves do not provide adequate protection for this product, the registrant should indicate a specific glove category from the EPA chemical resistance glove selection chart that will provide adequate protection.

First Aid:

If in eyes:
-Hold eye open and rinse slowly and gently with water for 15-20 minutes.
-Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
-Call a poison control center or doctor for treatment advice.

If on skin:
-Take off contaminated clothing.
-Rinse skin immediately with plenty of water for 15-20 minutes.
-Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: Note to PM/Registrant: The proposed label should contain a Note to Physician which addresses the category I Primary Eye Irritant toxicity. The following statements are suggested types of information that may be included, if applicable:

- technical information on symptomatology;
- use of supportive treatments to maintain life functions;
- medicine that will counteract the specific physiological effects of the pesticide;
- company telephone number to specific medical personnel who can provide specialized medical advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

User Safety Recommendations:

Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove and wash contaminated clothing before reuse.

DATA EVALUATION RECORD

STUDY TYPE: ACUTE ORAL TOXICITY TESTING (870.1100 formerly §81-1)

Product Manager: 25 **Reviewer:** Eugenia McAndrew

TEST MATERIAL PURITY: MON 78481; 36.8% glyphosate acid (45.1% potassium salt of glyphosate) and 0.184% carfentrazone acid

CITATION: Bonnette, K. (2002) acute oral toxicity in rats with MON 78481. Springborn Laboratories, Inc., Spencerville, Ohio. Laboratory Report Number 3044.879. March 25, 2002. MRID 45705302. Unpublished.

SPONSOR: Monsanto Company, 800 N. Lindberg Blvd., St Louis, MO 63141

EXECUTIVE SUMMARY: In an acute oral toxicity study, five young adult, Hsd: Sprague Dawley SD rats/sex (Age: Males: 10 weeks; Females: 9 weeks; Weight: 322-338 g males; 205-220 g females; Source: Harlan Sprague Dawley, Inc., Indianapolis, IN) were given a single oral dose of MON 78481 (36.8% glyphosate acid [45.1% potassium salt of glyphosate] and 0.184% carfentrazone acid; Lot No. GLP-01111-11850-F; amber liquid) at 5000 mg/kg. The test substance was administered as received. Body weights were obtained prior to dosing on day 0 and on days 7 and 14. Animals were observed for clinical signs of toxicity and mortality for 14 days post dosing. A gross necropsy examination was performed on all animals at scheduled euthanasia.

Oral LD_{50} Males = > 5000 mg/kg (observed); Oral LD_{50} Females = > 5000 mg/kg (observed)

MON 78481 is classified as Toxicity Category IV based on the observed LD_{50} value in males and females.

All animals survived and gained weight during the study. Clinical signs included transient incidences of dark material around the facial area, urine/fecal stain, small feces, soft stools, decreased activity, decreased defecation, decreased food consumption, rough haircoat and unkempt appearance. The animals recovered from these symptoms by day 4. Necropsy revealed thickened stomach in 4/10 animals and adhesions in the body cavity in one animal. One animal also had a tab on the liver.

This study is classified as Acceptable (870.1100) and satisfies the guideline requirement for an acute oral study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

OBSERVATIONS: All animals survived and gained weight during the study. Clinical signs included transient incidences of dark material around the facial area, urine/fecal stain, small feces, soft stools, decreased activity, decreased defecation, decreased food consumption, rough haircoat and unkempt appearance. The animals recovered from these symptoms by day 4.

GROSS NECROPSY: Necropsy revealed thickened stomach in 4/10 animals and adhesions in the body cavity in one animal. One animal also had a tab on the liver.

DATA EVALUATION RECORD

STUDY TYPE: ACUTE DERMAL TOXICITY TESTING (870.1200 formerly §81-2)

TEST MATERIAL PURITY: MON 78481; 36.8% glyphosate acid (45.1% potassium salt of glyphosate) and 0.184% carfentrazone acid

CITATION: Bonnette, K. (2002) acute dermal toxicity in rats with MON 78481. Springborn Laboratories, Inc., Spencerville, Ohio. Laboratory Report Number 3044.880. March 15, 2002. MRID 45705303. Unpublished.

SPONSOR: Monsanto Company, 800 N. Lindberg Blvd., St Louis, MO 63141

EXECUTIVE SUMMARY: In an acute dermal toxicity study, five young adult, Hsd: Sprague Dawley SD rats/sex (Age: 9- 10 weeks; Weight: 328-353 g males; 193-222 g females; Source: Harlan Sprague Dawley, Inc., Indianapolis, IN) were dermally exposed to a single application of MON 78481 (36.8% glyphosate acid [45.1% potassium salt of glyphosate] and 0.184% carfentrazone acid; Lot No. GLP-01111-11850-F; amber liquid) at 5000 mg/kg (limit dose) for 24 hours. The test substance was applied to approximately 10% of the total body surface area. Body weights were obtained prior to dosing on day 0 and on days 7 and 14. Animals were observed for dermal irritation, clinical signs of toxicity and mortality daily for 14 days. A gross necropsy examination was performed on all animals at the time of scheduled euthanasia.

Dermal LD_{50} Males = > 5000 mg/kg (observed); Dermal LD_{50} Females = > 5000 mg/kg (observed)

MON 78481 is classified as Toxicity Category IV based on the observed LD_{50} value in both sexes.

All animals survived. Two males lost weight during the first week. All other animals gained weight. Clinical signs noted were dark material around the facial area, decreased defecation and urine stain. Dermal irritation including erythema, edema, desquamation and superficial lightening was observed at all test sites. No gross internal findings were observed at necropsy.

This study is classified as Acceptable (870.1200) and satisfies the guideline requirement for an acute dermal study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
5000	0/5	0/5	0/10

OBSERVATIONS: All animals survived. Two males lost weight during the first week . All other animals gained weight. Clinical signs noted were dark material around the facial area, decreased defecation and urine stain. Dermal irritation including erythema, edema, desquamation and superficial lightening was observed at all test sites.

GROSS NECROPSY: No gross internal findings were observed at necropsy.

DATA EVALUATION RECORD

STUDY TYPE: ACUTE INHALATION TOXICITY TESTING (870.1300 formerly §81-3)

TEST MATERIAL PURITY: MON 78481; 36.8% glyphosate acid (45.1% potassium salt of glyphosate) and 0.184% carfentrazone acid

CITATION: Bonnette, K. (2002) acute nose-only inhalation toxicity in rats with MON 78481. Springborn Laboratories, Inc., Spencerville, Ohio. Laboratory Report Number 3044.881. April 2, 2002. MRID 45705304. Unpublished.

SPONSOR: Monsanto Company, 800 N. Lindberg Blvd., St Louis, MO 63141

EXECUTIVE SUMMARY: In an acute inhalation toxicity study, five young adult Hsd: Sprague Dawley SD rats/sex (Age: 11-12 weeks; Weight: 360-427 g males; 214-234 g females; Source: Harlan Sprague Dawley, Inc., Indianapolis, IN) were exposed by nose-only inhalation to MON 78481 (36.8% glyphosate acid [45.1% potassium salt of glyphosate] and 0.184% carfentrazone acid; Lot No. GLP-01111-11850-F; amber liquid) at 2.62 mg/L for 4 hours. Body weights were obtained prior to dosing on day 0 and on days 7 and 14. All animals were observed for clinical signs of toxicity and mortality during the exposure and for 14 days post exposure. Gross necropsies were performed on all animals.

Inhalation LC_{50} Males = > 2.62 mg/L (observed); Inhalation LC_{50} Females = > 2.62 mg/L (observed)

MON 78481 is classified as Toxicity Category IV based on the observed LC_{50} values in both sexes.

All animals survived the exposure. One female and four males lost weight during the first week and one female lost weight during the second week. All other animals gained weight during the study. All animals exceeded initial body weight by study termination. Clinical signs noted were congested breathing, decreased defecation, rough haircoat, and dark material around the facial area and nasal discharge. The animals recovered from these symptoms by day 12. The analytical chamber concentration was 2.62 mg/L. The mass median aerodynamic diameter was 3.0 µm with a geometric standard deviation of 1.87. No gross internal findings were noted at necropsy.

This study is classified as Acceptable (870.1300) and satisfies the guideline requirement for an acute inhalation study in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS:

Exposure Concentration mg/L (Analytically Determined)	Number of Deaths/Number Tested		
	Males	Females	Combined
2.62	0/5	0/5	0/10

Chamber Atmosphere		
Exposure conc.	MMAD	GSD
2.62 mg/L	3.0 µm [a]	1.87

[a] 71% of the particles were ≤ 4.0 µm

Chamber Environment[a]	
Chamber Volume	10 L
Airflow	22 LPM
Temperature	72 °F
Relative Humidity	53-59 %

[a] nose only

OBSERVATIONS: All animals survived the exposure. One female and four males lost weight during the first week and one female lost weight during the second week. All other animals gained weight during the study. All animals exceeded initial body weight by study termination. Clinical signs noted were congested breathing, decreased defecation, rough haircoat, and dark material around the facial area and nasal discharge. The animals recovered from these symptoms by day 12. The analytical chamber concentration was 2.62 mg/L. The mass median aerodynamic diameter was 3.0 µm with a geometric standard deviation of 1.87.

GROSS NECROPSY: No gross internal findings were noted at necropsy.

DATA EVALUATION RECORD

STUDY TYPE: PRIMARY EYE IRRITATION TESTING (870.2400 formerly §81-4)

TEST MATERIAL PURITY: MON 78481; 36.8% glyphosate acid (45.1% potassium salt of glyphosate) and 0.184% carfentrazone acid

CITATION: Bonnette, K. (2002) primary eye irritation in rabbits with MON 78481. Springborn Laboratories, Inc., Spencerville, Ohio. Laboratory Report Number 3044.882. March 15, 2002. MRID 45705305. Unpublished.

SPONSOR: Monsanto Company, 800 N. Lindberg Blvd., St Louis, MO 63141

EXECUTIVE SUMMARY: In a primary eye irritation study, 0.1 mL of MON 78481 (36.8% glyphosate acid [45.1% potassium salt of glyphosate] and 0.184% carfentrazone acid; Lot No. GLP-01111-11850-F; amber liquid) was placed into the conjunctival sac of the right eye of three male adult New Zealand White rabbits (Source: Myrtle's Rabbitry, Thompson Station, TN). All animals were observed for ocular irritation at 1, 24, 48 and 72 hours and at 7, 10, 14, 21 and 28 days post-instillation.

MON 78481 is classified as Toxicity Category I based on the irreversible corneal opacity observed in one eye.

All eyes exhibited iritis and conjunctivitis at the one hour observation. By 24 hours, 2/3 eyes showed corneal opacity. The iritis resolved by day 14. The conjunctivitis resolved by day 21. Corneal opacity resolved in one eye by day 7 but persisted in one eye through day 28. Additional ocular findings included sloughing of the corneal epithelium in 3/3 eyes and slight dulling of the normal luster of the cornea, neovascularization and corneal mineralization in one eye.

This study is classified as Acceptable (870.2400) and satisfies the guideline requirement for a primary eye irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS:

Observations	Number "positive"/number tested								
	Hours				Days				
	1	24	48	72	7	10	14	21	28
Corneal Opacity	0/3	2/3	2/3	2/3	1/3	1/3	1/3	1/3	1/3
Iritis	3/3	2/3	1/3	1/3	1/3	1/3	0/3	0/3	0/3
Conjunctivae:									
Redness*	3/3	3/3	3/3	2/3	1/3	0/3	0/3	0/3	0/3
Chemosis*	2/3	1/3	1/3	1/3	1/3	1/3	1/3	0/3	0/3
Discharge*	1/3	2/3	2/3	1/3	0/3	0/3	0/3	0/3	0/3

*Score of 2 or more required to be considered "positive."

OBSERVATIONS: All eyes exhibited iritis and conjunctivitis at the one hour observation. By 24 hours, 2/3 eyes showed corneal opacity. The iritis resolved by day 14. The conjunctivitis resolved by day 21. Corneal opacity resolved in one eye by day 7 but persisted in one eye through day 28. Additional ocular findings included sloughing of the corneal epithelium in 3/3 eyes and slight dulling of the normal luster of the cornea, neovascularization and corneal mineralization in one eye.

DATA EVALUATION RECORD

STUDY TYPE: PRIMARY DERMAL IRRITATION TESTING (870.2500 formerly §81-5)

TEST MATERIAL PURITY: MON 78481; 36.8% glyphosate acid (45.1% potassium salt of glyphosate) and 0.184% carfentrazone acid

CITATION: Bonnette, K. (2002) primary skin irritation in rabbits with MON 78481. Springborn Laboratories, Inc., Spencerville, Ohio. Laboratory Report Number 3044.883. March 25, 2002. MRID 45705306. Unpublished.

SPONSOR: Monsanto Company, 800 N. Lindberg Blvd., St Louis, MO 63141

EXECUTIVE SUMMARY: In a primary skin irritation study, three adult New Zealand White rabbits (2 male and 1 female; Source: Myrtle's Rabbitry, Thompson Station, TN) were dermally exposed to 0.5 mL of MON 78481 (36.8% glyphosate acid [45.1% potassium salt of glyphosate] and 0.184% carfentrazone acid; Lot No. GLP-01111-11850-F; amber liquid) for 4 hours. The test substance was applied to a single 1 inch x 1 inch intact dose site on each animal and covered with a gauze patch. Animals were observed 1, 24, 48 and 72 hours and up to 21 days after patch removal.

MON 78481 is classified as Toxicity Category III based on the moderate irritation observed.

Primary Dermal Irritation Index (PDII) = 2.5 Well defined erythema was noted at all test sites and very slight edema at one site at the one hour scoring. At 72 hours, the well defined erythema was still present at all three sites with very slight edema also present. The irritation began to subside after 7 days. All sites were free of dermal irritation by day 21. Desquamation was noted at 3/3 sites and superficial lightening at 2/3 sites.

This study is classified as Acceptable (870.2500) and satisfies the guideline requirement for a primary skin irritation study in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

RESULTS: Primary Dermal Irritation Index (PDII) = 2.5

OBSERVATIONS: Well defined erythema was noted at all test sites and very slight edema at one site at the one hour scoring. At 72 hours, the well defined erythema was still present at all three sites with very slight edema also present. The irritation began to subside after 7 days. All sites were free of dermal irritation by day 21. Desquamation was noted at 3/3 sites and superficial lightening at 2/3 sites.

DATA EVALUATION RECORD

STUDY TYPE: DERMAL SENSITIZATION TESTING (870.2600 formerly §81-6)

TEST MATERIAL PURITY: MON 78481; 36.8% glyphosate acid (45.1% potassium salt of glyphosate) and 0.184% carfentrazone acid

CITATION: Bonnette, K. (2002) dermal sensitization in guinea pigs with MON 78481 Modified Buehler Design. Springborn Laboratories, Inc., Spencerville, Ohio. Laboratory Report Number 3044.884. April 4, 2002. MRID 45705307. Unpublished.

SPONSOR: Monsanto Company, 800 N. Lindberg Blvd., St Louis, MO 63141

EXECUTIVE SUMMARY: In a dermal sensitization study conducted with MON 78481 (36.8% glyphosate acid [45.1% potassium salt of glyphosate] and 0.184% carfentrazone acid; Lot No. GLP-01111-11850-F; amber liquid), 30 young adult male and female Hartley -derived albino guinea pigs (Age: males - 6 weeks; females - 8 weeks; Source: Hilltop Lab Animals, Inc., Scottdale, PA) were tested using a modified Buehler design. Preliminary testing was conducted with four animals to determine the correct concentrations for induction and challenge. In the main study, for the first induction, twenty test animals were induced with 0.3 mL of a 75% concentration of test substance in deionized water for a six hour exposure. "Based on the unanticipated low dermal response at Induction 1, this was increased to 100% for Inductions 2 and 3." The induction procedure was repeated on study day 7 and 14 for a total of three induction exposures. The animals rested for two weeks. On day 28, 0.3 mL of 75% test substance in deionized water (highest non-irritating concentration) was applied to the twenty test guinea pigs and to ten naive control guinea pigs for a six-hour challenge exposure. Reactions were scored 24 and 48 hours after each induction and after the challenge. A positive control study using α-hexylcinnamaldehyde (HCA) was conducted within six months of the main study to validate the test system.

MON 78481 is classified as a non-sensitizer based on the results of this study.

Dermal irritation after the first induction with 75% test substance in deionized water was limited to scores of ± (equivalent to 0.5) at 5/20 sites. Reactions after the second and third inductions with 100% test substance included scores of ± - 1 at all test animal sites with desquamation present at most sites. Following the challenge, dermal irritation noted in the test animals and in the naive control animals was similar with scores of 0 - ± . No positive scores were noted in either group. Based on these results, the test substance is not considered to be a contact sensitizer. The positive response observed in the HCA study validates the test system used in this study.

This study is classified as Acceptable (870.2600) and satisfies the guideline requirement for an dermal sensitization study in the guinea pig.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

PROCEDURE: In a dermal sensitization study conducted with MON 78481 (36.8% glyphosate acid [45.1% potassium salt of glyphosate] and 0.184% carfentrazone acid; Lot No. GLP-01111-11850-F; amber liquid), 30 young adult male and female Hartley -derived albino guinea pigs (Age: males - 6 weeks; females - 8 weeks; Source: Hilltop Lab Animals, Inc., Scottdale, PA) were tested using a modified Buehler design. Preliminary testing was conducted with four animals to determine the correct concentrations for induction and challenge. In the main study, for the first induction, twenty test animals were induced with 0.3 mL of a 75% concentration of test substance in deionized water for a six hour exposure. "Based on the unanticipated low dermal response at Induction 1, this was increased to 100% for Inductions 2 and 3." The induction procedure was repeated on study day 7 and 14 for a total of three induction exposures. The animals rested for two weeks. On day 28, 0.3 mL of 75% test substance in deionized water (highest non-irritating concentration) was applied to the twenty test guinea pigs and to ten naive control guinea pigs for a six-hour challenge exposure. Reactions were scored 24 and 48 hours after each induction and after the challenge. A positive control study using α-hexylcinnamaldehyde (HCA) was conducted within six months of the main study to validate the test system.

RESULTS: Dermal irritation after the first induction with 75% test substance in deionized water was limited to scores of ± (equivalent to 0.5) at 5/20 sites. Reactions after the second and third inductions with 100% test substance included scores of ± - 1 at all test animal sites with desquamation present at most sites. Following the challenge, dermal irritation noted in the test animals and in the naive control animals was similar with scores of 0 - ± . No positive scores were noted in either group. Based on these results, the test substance is not considered to be a contact sensitizer. The positive response observed in the HCA study validates the test system used in this study.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D284522
2. **PC CODE:** 103613, 128712
3. **CURRENT DATE:** 22/OCT/2002
4. **TEST MATERIAL:** MON 78481 (36.8% glyphosate acid [45.1% potassium salt of glyphosate] and 0.184% carfentrazone acid; Lot No. GLP-01111-11850-F; amber liquid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Springborn Laboratories, Inc. 3044.879/3-25-02	45705302	LD_{50} > 5000 mg/kg (males females combined)	IV	A
Acute dermal toxicity/rat Springborn Laboratories, Inc. 3044.880/3-15-02	45705303	LD_{50} > 5000 mg/kg (males females combined)	IV	A
Acute inhalation toxicity/rat Springborn Laboratories, Inc. 3044.881/4-2-02	45705304	LC_{50} > 2.62 mg/L (males females combined)	IV	A
Primary eye irritation/rabbit Springborn Laboratories, Inc. 3044.882/3-15-02	45705305	Corneal opacity, iritis and conjunctivitis in 3/3 eyes. Corneal opacity persisting in one eye through day 28.	I	A
Primary dermal irritation/rabbit Springborn Laboratories, Inc. 3044.883/3-25-02	45705306	PDII = 2.5 Moderate irritant	III	A
Dermal sensitization/guinea pig Springborn Laboratories, Inc. 3044.884/4-4-02	45705307	Non-sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**