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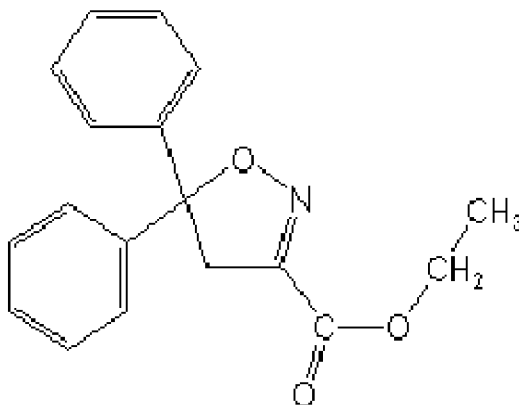
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(54) Title: NOVEL FORM OF ISOXADIFEN-ETHYL, PROCESS FOR PREPARATION AND USE THEREOF



(I)

(57) Abstract: A crystalline form of isoxadifen-ethyl of formula (I), the crystal preparation process, the analyses of the crystal through various analytical methods and using the crystal to prepare stable agrochemical formulation are provided. The use of various solvents towards the crystalline form preparation conditions is also provided.

NOVEL FORM OF ISOXADIFEN-ETHYL, PROCESS FOR PREPARATION AND USE THEREOF

Cross Reference of related application

The present application claims the priority of US Patent Application No. 14/926,377, filed on October 29, 2015, the contents of which are incorporated herein by reference in its entirety.

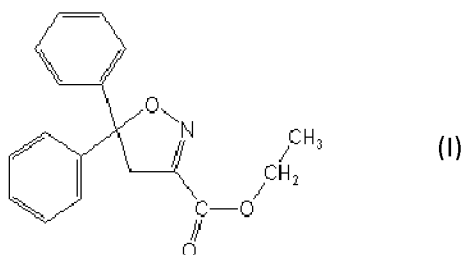
BACKGROUND

Field

The present disclosure relates to a crystalline form of ethyl 4,5-dihydro-5,5-diphenyl-3-isoxazolecarboxylate (isoxadifen-ethyl), to its preparation processes and to its use in agrochemical preparations.

Description of Related Art

Ethyl 4,5-dihydro-5,5-diphenyl-3-isoxazolecarboxylate (isoxadifen-ethyl) is a potent safener for sulfonylurea herbicides. Isoxadifen-ethyl has molecular formula of $C_{18}H_{17}NO_3$. Its chemical structure is:



It is typically used to reduce the phototoxicity of sulfonylurea herbicides when applied on crops, such as maize, wheat and cereals.

The commercially available isoxadifen-ethyl, which is usually manufactured by the process described in U.S. Patent No. 5,516,750, which is incorporated herein by reference for

all purposes, is present in an amorphous state, the melting point which is about 78°C -81°C.

SUMMARY

It has been found that isoxadifen-ethyl in amorphous state is highly unstable. It will generally undergo significant hydrolysis when dissolved or dispersed in water. Furthermore, hydrolysis can occur during storage, particularly where the compound is exposed to moisture. As a result, the stability of isoxadifen-ethyl is of great concern with respect to providing the commercially available formulations. Therefore, there is a need to provide a novel form of isoxadifen-ethyl with increased stability in formulations.

Accordingly, in an embodiment, the invention provides a novel crystalline form of isoxadifen-ethyl, termed “crystalline modification I”, and a process for its preparation, as well as agrochemical compositions containing it, and methods for using it in agrochemical applications, such as methods for applying it to plants, plant loci, and plant parts. The novel crystalline modification I has been found to have increased stability relative to the amorphous form. Accordingly, in an embodiment, the invention also provides compositions for controlling undesirable plant growth, such as weeds, comprising the crystalline modification I of isoxadifen-ethyl with sulfonylurea herbicides, as a mixture with auxiliaries and carriers. The use of the crystalline modification I of isoxadifen-ethyl with sulfonylurea herbicides in the control of undesired plant growth and a method for the same are also provided by embodiments of the invention.

BRIEF DESCRIPTION OF DRAWINGS

Various features and aspects of the embodiments of the invention disclosed herein can be more clearly understood by reference to the drawings, which are intended to exemplify and illustrate, but not to limit, the scope of the invention, and wherein:

FIG. 1 is an infrared (IR) spectra of an embodiment of crystalline modification I of isoxadifen-ethyl;

FIG. 2 is a powder X-ray diffractogram of an embodiment of crystalline modification I of isoxadifen-ethyl;

FIG. 3 is a graph showing the results of a Differential Scanning Calorimetry (DSC) scan of an embodiment of crystalline modification I of isoxadifen-ethyl; and

FIG. 4 is a graph showing the results of a powder X-ray diffractogram of amorphous isoxadifen-ethyl.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

The invention can be more clearly understood by reference to the following detailed description of specific embodiments thereof, which is intended to illustrate, but not limit, the scope of the appended claims.

It has been found that an embodiment of the crystalline modification I of isoxadifen-ethyl has a significant increase in its stability when mixing with sulfonylurea herbicides in formulations that are otherwise similar to current commercially available formulations, which contain the amorphous form of isoxadifen-ethyl. In addition, it has been found that the crystalline modification I of isoxadifen-ethyl is easier to comminute or grain compared to amorphous isoxadifen-ethyl prepared in accordance with the disclosure of U.S. Patent No. 5,516,750. This allows the preparation of commercial formulations such as suspension concentrates (SC), oil-based suspension concentrates (OD), water-dispersible granules (WG) and water-soluble granules (SG). Hence, it is possible to prepare any formulations of isoxadifen-ethyl in crystalline modification I when mixing with sulfonylurea herbicides, as will be disclosed hereinafter.

By virtue of its high stability, the crystalline modification I of isoxadifen-ethyl when mixing with sulfonylurea herbicides is highly suitable for preparing compositions for controlling undesirable weeds.

According to a first aspect of the invention, a crystalline modification I of isoxadifen-ethyl is provided, exhibiting at least 3 of the following reflexes as 2θ values, in any combination thereof, in an X-ray powder diffractogram recorded using Cu—K α radiation at 25 °C:

$$2\theta = 11.027 \pm 0.2 \quad (1)$$

$$2\theta = 17.841 \pm 0.2 \quad (2)$$

$$2\theta = 19.492 \pm 0.2 \quad (3)$$

$$2\theta = 19.841 \pm 0.2 \quad (4)$$

$$2\theta = 20.583 \pm 0.2 \quad (5)$$

- $2\theta = 22.151 \pm 0.2$ (6)
- $2\theta = 22.920 \pm 0.2$ (7)
- $2\theta = 23.541 \pm 0.2$ (8)
- $2\theta = 24.801 \pm 0.2$ (9)
- $2\theta = 25.775 \pm 0.2$ (10)
- $2\theta = 26.895 \pm 0.2$ (11)
- $2\theta = 27.813 \pm 0.2$ (12)
- $2\theta = 29.408 \pm 0.2$ (13)
- $2\theta = 30.065 \pm 0.2$ (14)
- $2\theta = 31.228 \pm 0.2$ (15)
- $2\theta = 33.502 \pm 0.2$ (16).

The crystalline modification I of isoxadifen-ethyl of an embodiment of the invention is characterized by an X-ray powder diffractogram having at least three of the reflexes indicated above, in any combination. This means that the crystalline modification I of an embodiment of isoxadifen-ethyl can contain 3 or more of the reflexes indicated above in any combination of reflexes. For example, the crystalline modification I of an embodiment of isoxadifen-ethyl can contain at least reflexes (1), (2), and (3), or at least reflexes (2), (3), and (4), or reflexes (1), (3), and (4), or any other combination of at least three reflexes. Preferably, the crystalline modification I is one having at least four of the aforementioned reflexes, more preferably at least five, six or seven, or eight of said reflexes, again in any combination. An X-ray powder diffractogram of the crystalline modification I of isoxadifen-ethyl is shown in Figure 2, which will be described in detail hereinafter.

According to a preferred embodiment the crystalline form A exhibits at least 3, 4, or 5 or all of the reflexes, in any combination, from the following:

- $2\theta = 11.027 \pm 0.2$ (1)
- $2\theta = 17.841 \pm 0.2$ (2)
- $2\theta = 19.492 \pm 0.2$ (3)

$$2\theta = 19.841 \pm 0.2 \quad (4)$$

$$2\theta = 24.801 \pm 0.2 \quad (9)$$

$$2\theta = 25.775 \pm 0.2 \quad (10)$$

$$2\theta = 26.895 \pm 0.2 \quad (11)$$

$$2\theta = 27.813 \pm 0.2 \quad (12).$$

The crystalline modification I of isoxadifen-ethyl according to an embodiment of the invention may be further characterized by Infrared (IR) spectroscopy. The IR spectrum of the crystalline modification I is showed in Figure 1 with characteristic bands at one or more of 2984.31, 2928.19, 2160.89, 1978.81 and 1716.65 cm^{-1} .

All IR spectra were obtained using the following acquisition parameters:

FT-IR spectrometer	Bruker Tensor37
Diamond ATR unit	from Specac
Wavelength range	550 - 4000 cm^{-1}
Resolution	4 cm^{-1}
Number of scans	16

The crystalline modification I of isoxadifen-ethyl according to an embodiment of the invention may be further characterized by differential scanning calorimetry (DSC) (Figure 3). The DSC spectrum of the crystalline modification I of isoxadifen-ethyl exhibits an endothermic peak at 86.5 °C as shown in Figure 3.

Methods for preparing amorphous isoxadifen-ethyl are known in the art. Amorphous isoxadifen-ethyl is manufactured and available on a commercial scale. A particularly suitable method for preparing amorphous isoxadifen-ethyl is described in U.S. Patent No. 5,516,750.

According to an embodiment of the invention, the crystalline modification I of

isoxadifen-ethyl can be obtained by the processes below:

Isxadifen-ethyl in amorphous state is dissolved and then crystallized from solvents.

In one aspect, the present invention provides a process for preparing a crystalline modification I of isoxadifen-ethyl comprising steps of:

- i) preparing a solution of an amorphous isoxadifen-ethyl in a solvent;
- ii) effecting crystallization of isoxadifen-ethyl from the solution to obtain a solid precipitate; and
- iii) isolating the solid precipitate.

Suitable solvents for preparing isoxadifen-ethyl crystalline modification I include acetonitrile, halogenated hydrocarbons (for example, chlorobenzene, bromobenzene, dichlorobenzene, chlorotoluene and trichlorobenzene), ethers (for example, ethyl propyl ether, n-butyl ether, anisole, phenetole, cyclohexyl methyl ether, dimethyl ether, diethyl ether, dimethyl glycol, diphenyl ether, dipropyl ether, diisopropyl ether, di-n-butyl ether, diisobutyl ether, diisoamyl ether, ethylene glycol dimethyl ether, isopropyl ethyl ether, methyl tert-butyl ether, tetrahydrofuran, methyltetrahydrofuran, dioxane, dichlorodiethyl ether, methyl-tetrahydrofuran, polyethers of ethylene oxide and/or propylene oxide), nitrated hydrocarbons (for example, nitromethane, nitroethane, nitropropane, nitrobenzene, chloronitrobenzene and o-nitrotoluene), aliphatic, cycloaliphatic or aromatic hydrocarbons (for example, pentane, n-hexane, n-heptane, n-octane, nonane), cymene, petroleum fractions having a boiling range of from 70 °C to 190 °C, cyclohexane, methylcyclohexane, petroleum ether, ligroin, octane, benzene, toluene and xylene), esters (for example, malonates, acetic acid n-butyl ester (n-butyl acetate), methyl acetate, ethyl acetate, isobutyl acetate, dimethyl carbonate, diethyl carbonate, dibutyl carbonate and ethylene carbonate), and aliphatic alcohols (for example, methanol, ethanol, n-propanol, isopropanol, n-butanol and tert-amyl alcohol), and mixtures of any of these.

Preferred solvents include acetonitrile, ethers, aromatic hydrocarbons (such as benzene, toluene, xylene, chlorobenzene), esters and aliphatic alcohols and mixtures thereof. Particularly preferred solvents or solvent mixtures include isopropanol, toluene, methyl-tetrahydrofuran, diethyl carbonate, chlorobenzene, n-butyl acetate, isobutyl acetate, n-butanol, methanol, ethanol, ethyl malonate, methyl t-butyl ether, and mixtures of these, particularly mixtures of toluene and butanol, mixtures of toluene and n-butyl acetate,

mixtures of ethyl malonate and methyl t-butyl ether, as well as mixtures of butyl acetate and methyl t-butyl ether. Solvent mixtures of more than 2 or 3 or 4 components are also envisaged by embodiments of the invention.

In the invention, it is preferred that the solvent comprises an alcohol and/or acetonitrile, including mixtures thereof, with other solvents or particularly with each other.

Hence, according to a preferred embodiment in step (i), amorphous isoxadifen-ethyl is dissolved in a solvent comprising methanol, or acetonitrile, or a mixture thereof.

In step (ii), isoxadifen-ethyl is crystallized from the solution. Techniques for effecting crystallization of isoxadifen-ethyl from the solution are known to those skilled in the art. For example, in an embodiment where the solution in step (i) is formed at elevated temperatures, crystallization may be effected by cooling the solution to room or ambient temperature. In one preferred embodiment, crystallization is effected by concentrating the solution formed in step (i) of the process by removal of solvent. Alternatively, or in addition thereto, seed crystals, in particular seed crystals of the aforementioned crystalline modification I of isoxadifen-ethyl, may be added to the solution formed in step (i), to facilitate and/or enhance crystallization.

It is preferred that the solid precipitate of isoxadifen-ethyl recovered during the crystallization stage is washed with a solvent for one or more times. Preferably, the solvent employed in the washing stage consists of one or more components of the solvent employed for forming the solution in step (i), as described hereinbefore. Methanol and acetonitrile, and mixtures thereof are particularly suitable solvents for washing the recovered solid of isoxadifen-ethyl.

The invention, in an embodiment, also relates to a composition comprising the crystalline modification I of isoxadifen-ethyl and a herbicidally effective amount of sulfonylurea herbicides. The weight ratio of the isoxadifen-ethyl to sulfonylurea herbicides varies within wide limits and is preferably in a range of about 1:10 to about 10:1, in particular in a range of about 1:10 to about 5:1.

The amount of sulfonylurea herbicides in the formulation can be less than about 70% by weight of the formulation, preferably less than about 50% by weight of the formulation, particularly preferably about 25% by weight of the formulation.

The use of amorphous isoxadifen-ethyl as a safener for sulfonylurea herbicides is

known in the art and is used on a commercial scale. The crystalline modification I of isoxadifen-ethyl is also active in reducing the phototoxicity of sulfonylurea herbicides when controlling weeds. Techniques of formulating and applying amorphous isoxadifen-ethyl and sulfonylurea herbicides are known in the art. Isoxadifen-ethyl in the crystalline modification I of the present invention may be formulated and applied in an analogous manner with sulfonylurea herbicides.

Accordingly, in a further aspect, the invention provides a herbicidal composition comprising isoxadifen-ethyl in the crystalline modification I, as defined hereinbefore, with sulfonylurea herbicides.

Accordingly, an embodiment of the invention furthermore provides processes for preparing compositions for controlling weeds using the crystalline modification I of isoxadifen-ethyl together with sulfonylurea herbicides.

The crystalline modification I of isoxadifen-ethyl together with sulfonylurea herbicides can be incorporated in a known manner to the customary formulations, such as suspension concentrates (SC), oil-based suspension concentrates (OD), water-soluble granules (SG), dispersible concentrates (DC), emulsifiable concentrates (EC), emulsion seed dressings, suspension seed dressings, granules (GR), microgranules (MG), suspoemulsions (SE) and water-dispersible granules (WG) using herbicidally acceptable auxiliaries, carriers and solvents.

These formulations are prepared by mixing the crystalline modification I of isoxadifen-ethyl and sulfonylurea herbicides in amounts of each analogous to those used for amorphous isoxadifen-ethyl with customary additives, for example, liquid diluents, solid diluents, wetting agents, dispersants, thickening agents, antifoaming agent and other formulation ingredients.

Sulfonylurea herbicides suitable for safening by the crystalline modification I of isoxadifen-ethyl include, but are not limited to, amidosulfuron, azimsulfuron, bensulfuron-methyl, chlorimuron-ethyl, chlorsulfuron, cinosulfuron, cyclosulfamuron, ethametsulfuron-methyl, ethoxysulfuron, flupyrsulfuron-methyl, flazasulfuron, foramsulfuron, halosulfuron-methyl, imazosulfuron, iodosulfuron-methyl, mesosulfuron-methyl, metsulfuron-methyl, nicosulfuron, oxasulfuron, primisulfuron-methyl, prosulfuron,

pyrazosulfuron-ethyl, rimsulfuron, sulfometuron-methyl, sulfosulfuron, thifensulfuron-methyl, triasulfuron, tribenuron-methyl, trifloxysulfuron, triflusulfuron-methyl, tritosulfuron and salts thereof, and mixtures thereof.

The following sulfonylureas are preferred for safening by the crystalline modification I of isoxadifen-ethyl in accordance with an embodiment of the invention: bensulfuron-methyl, flupyrsulfuron-methyl, metsulfuron-methyl, nicosulfuron, rimsulfuron, sulfometuron-methyl, thifensulfuron-methyl, tribenuron-methyl, halosulfuron-methyl, iodosulfuron-methyl, mesosulfuron-methyl and salts thereof, and mixtures thereof.

Liquid diluents include, but are not limited to, water, N,N-dimethylamide, dimethyl sulfoxide, N-alkylpyrrolidone, ethylene glycol, polypropylene glycol, propylene carbonate, dibasic esters, paraffines, alkylbenzenes, alkyl naphthalenes, glycerine, triacetine, oils of olive, castor, linseed, sesame, corn, peanut, cotton-seed, soybean, rape-seed and coconut, ketones such as cyclohexanone, 2-heptanone, isophorone and 4-hydroxy-4-methyl-2-pentanone, acetates such as hexyl acetate, heptyl acetate and octyl acetate, and alcohols such methanol, cyclohexanol, decanol, benzyl and tetrahydrofurfuryl alcohol, and mixtures of these.

Solid diluents can be water-soluble or water-insoluble. Water-soluble solid diluents include, but are not limited to, salts such as alkali metal phosphates (e.g., sodium dihydrogen phosphate), alkaline earth phosphates, sulfates of sodium, potassium, magnesium and zinc, sodium and potassium chloride, sodium acetate, sodium carbonate and sodium benzoate, and sugars and sugar derivatives such as sorbitol, lactose, sucrose and mannitol, and mixtures thereof. Examples of water-insoluble solid diluents include, but are not limited to clays, synthetic and diatomaceous silicas, calcium and magnesium silicates, titanium dioxide, aluminum, calcium and zinc oxide, and mixtures of these.

Wetting agents include, but are not limited to, alkyl sulfosuccinates, laureates, alkyl sulfates, phosphate esters, acetylenic diols, ethoxyfluorinated alcohols, ethoxylated silicones, alkyl phenol ethoxylates, benzene sulfonates, alkyl-substituted benzene sulfonates, alkyl α -olefin sulfonates, naphthalene sulfonates, alkyl-substituted naphthalene sulfonates, condensates of naphthalene sulfonates and alkyl-substituted naphthalene sulfonates with

formaldehyde, and alcohol ethoxylates, and mixtures of these. Alkyl naphthalene sulphonates, sodium salts are particularly useful for the composition of the invention

Dispersants include, but are not limited to, sodium, calcium and ammonium salts of ligninsulfonates (optionally polyethoxylated); sodium and ammonium salts of maleic anhydride copolymers; sodium salts of condensed phenolsulfonic acid; and naphthalene sulfonate-formaldehyde condensates, and mixtures of these. Ligninsulfonates such as sodium ligninsulfonates are particularly useful for the composition of the invention. Naphthalene sulfonate-formaldehyde condensates, such as naphthalenesulfonic acid, polymers with formaldehyde, and sodium salts are particularly useful for the composition of an embodiment of the invention

Thickening agents include, but are not limited to, guar gum, pectin, casein, carrageenan, xanthan gum, alginates, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose, and mixtures of these. Synthetic thickening agents include derivatives of the former categories, and also polyvinyl alcohols, polyacrylamides, polyvinylpyrrolidones, various polyethers, their copolymers as well as polyacrylic acids and their salts, and mixtures of these. Alkylpolyvinylpyrrolidones are particularly useful for the composition of the present invention

Other formulation ingredients can also be used in the present invention such as dyes, defoamers, drying agents, and the like. These ingredients are known to one skilled in the art.

The crystalline modification I of isoxadifen-ethyl according to an embodiment of the invention can be present in formulations and in its use forms, prepared from these formulations, and as a safener to reduce the phototoxicity of sulfonylurea herbicides.

All plants, plant parts, and plant loci can be treated in accordance with the invention. In the present context, plants are to be understood as meaning all plants and plant populations such as desired and undesired wild plants or crop plants (including naturally occurring crop plants). Crop plants can be plants which can be obtained by conventional breeding and optimization methods, by biotechnological and genetic engineering methods, or by combinations of these methods, including the transgenic plants and the plant cultivars which can or cannot be protected by plant breeders' rights. Plant parts are to be understood as meaning all parts and organs of plants above and below the ground, such as shoot, leaves, needles, stalks,

stems, flowers, fruit bodies, fruits, seeds, roots, tubers and rhizomes. Harvested materials, and vegetative and generative propagation materials, for example, cutting, tubers, meristem tissue, rhizomes, offsets, seeds, single and multiple plant cells and any other plant tissues, are also included. Loci of plants include the environment near the plant and/or plant propagation materials, such as the soil in which the plant grows or will be sown, or the plant's surroundings.

As used herein, the term “about,” when used in connection with a numerical amount or range, means somewhat more or somewhat less than the stated numerical amount or range, to a deviation of $\pm 10\%$ of the stated numerical amount or endpoint of the range.

The term “herbicidally effective amount” as used herein, refers to the quantity of such a compound or combination of such compounds that is capable of producing a controlling effect on the growth of plants. The controlling effects include all deviation from the natural development of the target plants, for example killing, retardation of one or more aspects of the development and growth of the plant, leaf burn, albinism, dwarfing and the like. Treatment of the plants and plant parts with the compositions or formulations of the inventions according to the invention is carried out directly or by allowing the compositions or formulations to act on their loci, habitat or storage space by the customary treatment methods. Examples of these customary treatment methods include dipping, spraying, vaporizing, fogging, broadcasting, painting on in the case of propagation material, and applying one or more coats particularly in the case of seed.

The benefits of the invention are seen most when the herbicidal composition is applied to kill weeds in growing crops of useful plants, such as maize (corn) including field corns, pop corns and sweet corns, cotton, wheat, barley, rye, triticale, rice, oats, potatoes, sugar beets, plantation crops (such as bananas, fruit trees, rubber trees, tree nurseries), vines, asparagus, bushberries (such as blueberries), caneberries, cranberries, flax, grain sorghum, okra, peppermint, rhubarb, spearmint and sugarcane. In this invention, treatment of growing crops of maize and potatoes are particularly beneficial.

All percentages are given in weight % unless otherwise indicated.

Embodiments of the invention will now be described by way of the following examples which are provided for illustrative purposes only, and not intended to limit the scope of the disclosure or of the appended claims.

Examples

Example 1: Preparation of amorphous isoxadifen-ethyl in accordance with the disclosure of U.S. Patent No. 5,516,750

13.52 g (0.075 mol) of 1,1-diphenylethene and 5.06 g (0.05 mol) of triethylamine are dissolved in 200 ml of ether at 0 °C, and 7.58 g (0.05 mol) of ethyl 2-chloro-2-hydroximinoacetate, dissolved in 100 ml of ether, are subsequently added dropwise in the course of approximately two hours. After stirring has been continued for one hour at room temperature, 100 ml of H₂O are added, and the mixture is subsequently extracted using ether. After drying over a MgSO₄, the ether is distilled off and the residue is purified over a silica gel column (eluent: n-heptane:ethyl acetate=8:2). In this way, 12.7 g of product of melting point 78 °C to 81 °C are obtained.

As shown in Figure 4, the X-ray powder diffraction pattern of the resulting isoxadifen-ethyl products prepared above has no significant signals, which indicates the isoxadifen-ethyl product prepared in accordance with the disclosure of U.S. Patent No. 5,516,750 is amorphous.

Example 2: Preparation of the crystalline modification I of isoxadifen-ethyl

Crystallization from methanol

10ml methanol was charged into the reactor to dissolve crude, amorphous isoxadifen-ethyl prepared in Example 1 under stirring. This process lasted for 2 hours under room temperature, and white solid precipitate appeared. The mixture was then cooled down to 0 °C - 5 °C and maintained at this temperature for 1 hour to allow complete crystallization. After that, the mixture was centrifuged. The filter cake was washed with methanol. The resulting solid was dried under high vacuum to give crystals of pure isoxadifen-ethyl technical (Purity: 98%).

The crystals were characterized as being of the crystalline modification I of isoxadifen-ethyl using both IR spectrometry, X-ray powder diffraction and DSC.

The IR spectrum of the crystalline modification I of isoxadifen-ethyl is set out in Figure

1. The IR spectrum exhibits characteristic peaks at 2984.31, 2928.19, 2160.89, 1978.81 and 1716.65 cm^{-1} .

The melting point of the product was measured by DSC and exhibits a peak at 86.5 °C as shown in Figure 3.

The crystalline modification I of isoxadifen-ethyl has the X-ray powder diffractogram shown in Figure 2 with the reflexes listed in Table 1 below.

Table 1

Crystalline modification I	
2 θ (°)	d (Å)
11.027 $\pm$ 0.2	9.31 $\pm$ 0.05
17.841 $\pm$ 0.2	5.77 $\pm$ 0.05
19.492 $\pm$ 0.2	5.28 $\pm$ 0.05
19.841 $\pm$ 0.2	5.19 $\pm$ 0.05
24.801 $\pm$ 0.2	4.17 $\pm$ 0.05
25.775 $\pm$ 0.2	4.01 $\pm$ 0.05
26.895 $\pm$ 0.2	3.85 $\pm$ 0.05
27.813 $\pm$ 0.2	3.72 $\pm$ 0.05

Example 3: Preparation of the crystalline modification I of isoxadifen-ethyl

Crystallization from acetonitrile

10ml acetonitrile was charged into the reactor to dissolve crude, amorphous isoxadifen-ethyl prepared in Example 1 under stirring. This process lasted for 2 hours under room temperature, and white solid precipitate appeared. The mixture was then cooled down to 0 °C - 5 °C and maintained at this temperature for 1 hour to allow complete crystallization. After that, the mixture was centrifuged. The filter cake was washed with some acetonitrile. The resulting solid was dried under high vacuum to give crystals of pure isoxadifen-ethyl technical (Purity: 98%).

The crystals were characterized as being the crystalline modification I of isoxadifen-ethyl using IR spectrometry, X-ray powder diffraction and DSC as described in Example 2.

Example 4: Preparation of oil based suspension concentrate (OD) formulation

All the components listed in Table 2 below were mixed uniformly and ground with a Dyno-Mill (manufactured by Willy A. Bachofen AG) to obtain an oil based suspension concentrate.

Table 2

Ingredients	Weights %		Function
Isoxadifen-ethyl, crystalline modification I, 98% (prepared in Example 2)	10.20	0.00	Safener
Amorphous isoxadifen-ethyl (prepared in Example 1)	0.00	10.20	Safener
Tribenuron-methyl, 98%	40.80	40.80	Active compound
Sodium lignosulfonate (REAX [®] 88B)	12.00	12.00	Dispersing agent
Alkylpolyvinylpyrrolidone	10.00	10.00	Thickening agent
Corn oil	Balance to 100%	Balance to 100%	Carrier

Example 5: Preparation of soluble granules (SG)

All the components listed in Table 3 below were mixed, blended and milled in a high-speed rotary mill. Sufficient water was added to obtain an extrudable paste. The paste was extruded through a die or screen to form an extrudate. The wet extrudate was dried at 70° C in a vacuum oven and then sifted through 0.71 mm – 2 mm screens to obtain the product granules.

Table 3

Ingredients	Weights %		Function
Isoxadifen-ethyl, crystalline	7.14	0.00	Safener

modification I, 98% (prepared in Example 2)			
Amorphous isoxadifen-ethyl (prepared in Example 1)	0.00	7.14	Safener
Metsulfuron-methyl, 98%	25.51	25.51	Active compound
Lignosulfonic acid, sodium salt, (REAX [®] 88B)	15.00	15.00	Dispersing agent
Naphthalenesulfonic acid, polymer with formaldehyde, sodium salt (TAMOL [®] NN 8906)	6.00	6.00	Dispersing agent
Sodium acetate	4.00	4.00	Filler
Sodium carbonate	4.00	4.00	Filler
Non-ionic aqueous emulsion of Polydimethylsiloxanes	1.00	1.00	Antifoaming agent
Mannitol	Balance to 100%	Balance to 100%	carrier

Example 6: Preparation of water dispersible granules (WG)

All the components listed in Table 4 below were mixed, blended and milled in a high-speed rotary mill. Sufficient water was added to obtain an extrudable paste. The paste was extruded through a die or screen to form an extrudate. The wet extrudate was dried at 70°C in a vacuum oven and then sifted through 0.71 mm – 2 mm screens to obtain the product granules.

Table 4

Ingredients	Weights %		Function
Isoxadifen-ethyl, crystalline modification I, 98% (prepared in Example 2)	7.14	0.00	Safener
Amorphous isoxadifen-ethyl (prepared in Example 1)	0.00	7.14	Safener
Metsulfuron-methyl, 98%	25.51	25.51	Active compound

Alkyl naphthalene sulphonate, sodium salt (Akzo Nobel)	2	2	Wetting agent
Lignosulfonic acid, sodium salt, REAX [®] 88B)	15	15	Dispersing agent
Naphthalenesulfonic acid, polymer with formaldehyde, sodium salt (TAMOL [®] NN8906)	6	6	Dispersing agent
Sucrose	10	10	Filler
Non-ionic aqueous emulsion of Polydimethylsiloxanes	1	1	Antifoaming agent
Mannitol	Balance to 100%	Balance to 100%	Carrier

Example 7: Stability test

The stability of the isoxadifen-ethyl in these compositions was determined by aging samples in heated ovens having the same atmosphere therein, and then comparing the isoxadifen-ethyl content before and after aging to determine relative percentage of hydrolysis (RPH). RPH was calculated by the following equation:

$$\text{RPH} = \frac{(\text{The final weight \% of isoxadifen - ethyl} - \text{The initial weight \% of isoxadifen - ethyl})}{\text{The initial weight \% of isoxadifen - ethyl}} \times 100\%$$

Isoxadifen-ethyl content was determined by assaying the compositions with high-pressure liquid chromatography (HPLC) using reverse phase columns and eluants.

Samples prepared in Examples 4, 5 and 6 were stored at 54 °C for 1 week. The procedures are followed according to CIPAC MT 46.3. The concentration of isoxadifen-ethyl was measured at the end of each storage time by HPLC. The results are listed in Table 5.

Table 5

Sample	Compound	Weight (%) of Isoxadifen-ethyl	RPH%
Example 4	Isoxadifen-ethyl, crystalline	10	0

	modification I		
	Amorphous isoxadifen-ethyl	10	-50
Example 5	Isoxadifen-ethyl, crystalline modification I	7	0
	Amorphous isoxadifen-ethyl	7	-40
Example 6	Isoxadifen-ethyl, crystalline modification I	7	0
	Amorphous isoxadifen-ethyl	7	-45

CLAIMS

1. A crystalline modification I of isoxadifen-ethyl, exhibiting at least 3 of the following reflexes, in any combination, in an X-ray powder diffractogram recorded using Cu—K α radiation at 25 °C:

$$2\theta = 11.027 \pm 0.2 \quad (1)$$

$$2\theta = 17.841 \pm 0.2 \quad (2)$$

$$2\theta = 19.492 \pm 0.2 \quad (3)$$

$$2\theta = 19.841 \pm 0.2 \quad (4)$$

$$2\theta = 20.583 \pm 0.2 \quad (5)$$

$$2\theta = 22.151 \pm 0.2 \quad (6)$$

$$2\theta = 22.920 \pm 0.2 \quad (7)$$

$$2\theta = 23.541 \pm 0.2 \quad (8)$$

$$2\theta = 24.801 \pm 0.2 \quad (9)$$

$$2\theta = 25.775 \pm 0.2 \quad (10)$$

$$2\theta = 26.895 \pm 0.2 \quad (11)$$

$$2\theta = 27.813 \pm 0.2 \quad (12)$$

$$2\theta = 29.408 \pm 0.2 \quad (13)$$

$$2\theta = 30.065 \pm 0.2 \quad (14)$$

$$2\theta = 31.228 \pm 0.2 \quad (15)$$

$$2\theta = 33.502 \pm 0.2 \quad (16).$$

2. The crystalline modification I of isoxadifen-ethyl according to claim 1, exhibiting at least 3 of the following reflexes, in any combination, in an X-ray powder diffractogram recorded using Cu—K α radiation at 25 °C:

$$2\theta = 11.027 \pm 0.2 \quad (1)$$

$$2\theta = 17.841 \pm 0.2 \quad (2)$$

$$2\theta = 19.492 \pm 0.2 \quad (3)$$

$$2\theta = 19.841 \pm 0.2 \quad (4)$$

$$2\theta = 24.801 \pm 0.2 \quad (9)$$

$$2\theta = 25.775 \pm 0.2 \quad (10)$$

$$2\theta = 26.895 \pm 0.2 \quad (11)$$

$$2\theta = 27.813 \pm 0.2 \quad (12).$$

3. The crystalline modification I of isoxadifen-ethyl according to claim 1, exhibiting at least four of said reflexes, in any combination.

4. The crystalline modification I of isoxadifen-ethyl according to claim 1, exhibiting at least five of said reflexes, in any combination.

5. The crystalline modification I of isoxadifen-ethyl according to claim 1, exhibiting an IR spectrum with one or more of the characteristic bands at 2984.31, 2928.19, 2160.89, 1978.81 and 1716.65 cm^{-1} .

6. The crystalline modification I of isoxadifen-ethyl according to claim 1, exhibiting a DSC spectrum having an endothermic peak at 86.5°C .

7. A process for the preparation of a crystalline modification I of isoxadifen-ethyl according to claim 1, comprising:

- i) preparing a solution of an amorphous isoxadifen-ethyl in a solvent;
- ii) effecting crystallization of isoxadifen-ethyl from the solution to obtain a solid precipitate; and
- iii) isolating the solid precipitate.

8. The process according to claim 7, wherein the solvent comprises an alcohol, acetonitrile, or a combination thereof.

9. The process according to Claim 8, wherein the solvent is methanol, acetonitrile, or a mixture thereof.

10. A composition comprising a safening amount of the crystalline modification I of isoxadifen-ethyl according to claim 1, a herbicidally effective amount of at least one sulfonylurea herbicide, and at least one herbicidally acceptable auxiliary.

11. The composition in claim 10, in the form of a suspension concentrate (SC), an oil-based suspension concentrate (OD), a water-soluble granule (SG), a dispersible

concentrate (DC), an emulsifiable concentrate (EC), an emulsion seed dressing, a suspension seed dressing, a granule (GR), a microgranule (MG), a suspoemulsion (SE) or a water-dispersible granule (WG).

12. The composition according to claim 11, in the form of an oil-based suspension concentrate (OD).

13. The composition according to claim 11, in the form of a water-soluble granule (SG).

14. The composition according to claim 11, in the form of a water-dispersible granule (WG).

15. The composition according to claim 10, wherein the auxiliary is selected from one or more of a solvent, a diluent, a wetting agent, a dispersant, and a thickening agent and an antifoaming agent.

16. The composition according to claim 10, where the weight ratio of the isoxadifen-ethyl to sulfonylurea herbicides is in a range of about 1:10 to about 10:1, in particular in a range of about 1:10 to about 5:1.

17. A method of controlling unwanted plant growth, comprising applying to the plant an effective amount of a composition according to claim 10.

18. The composition according to claim 10, wherein the sulfonylurea herbicide comprises one or more selected from the group consisting of amidosulfuron, azimsulfuron, bensulfuron-methyl, chlorimuron-ethyl, chlorsulfuron, cinosulfuron, cyclosulfamuron, ethametsulfuron-methyl, ethoxysulfuron, flupyrsulfuron-methyl, flazasulfuron, foramsulfuron, halosulfuron-methyl, imazosulfuron, iodosulfuron-methyl, mesosulfuron-methyl, metsulfuron-methyl, nicosulfuron, oxasulfuron, primisulfuron-methyl, prosulfuron, pyrazosulfuron-ethyl, rimsulfuron, sulfometuron-methyl, sulfosulfuron, thifensulfuron-methyl, triasulfuron, tribenuron-methyl, trifloxysulfuron, triflusulfuron-methyl, tritosulfuron and salts thereof, and mixtures thereof.

19. The composition according to claim 18, wherein the sulfonylurea herbicide comprises one or more selected from the group consisting of bensulfuron-methyl, flupyrsulfuron-methyl, metsulfuron-methyl, nicosulfuron, rimsulfuron, sulfometuron-methyl, thifensulfuron-methyl, tribenuron-methyl, halosulfuron-methyl, iodosulfuron-methyl, mesosulfuron-methyl and salts thereof, and mixtures thereof.

20. Crystalline modification I of isoxadifen-ethyl substantially as hereinbefore described having reference to either of Figures 1 or 2.

21. A process for preparing modification I of isoxadifen-ethyl substantially as hereinbefore described.

22. A composition comprising modification I of isoxadifen-ethyl substantially as hereinbefore described.

23. A use of modification I of isoxadifen-ethyl substantially as hereinbefore described.

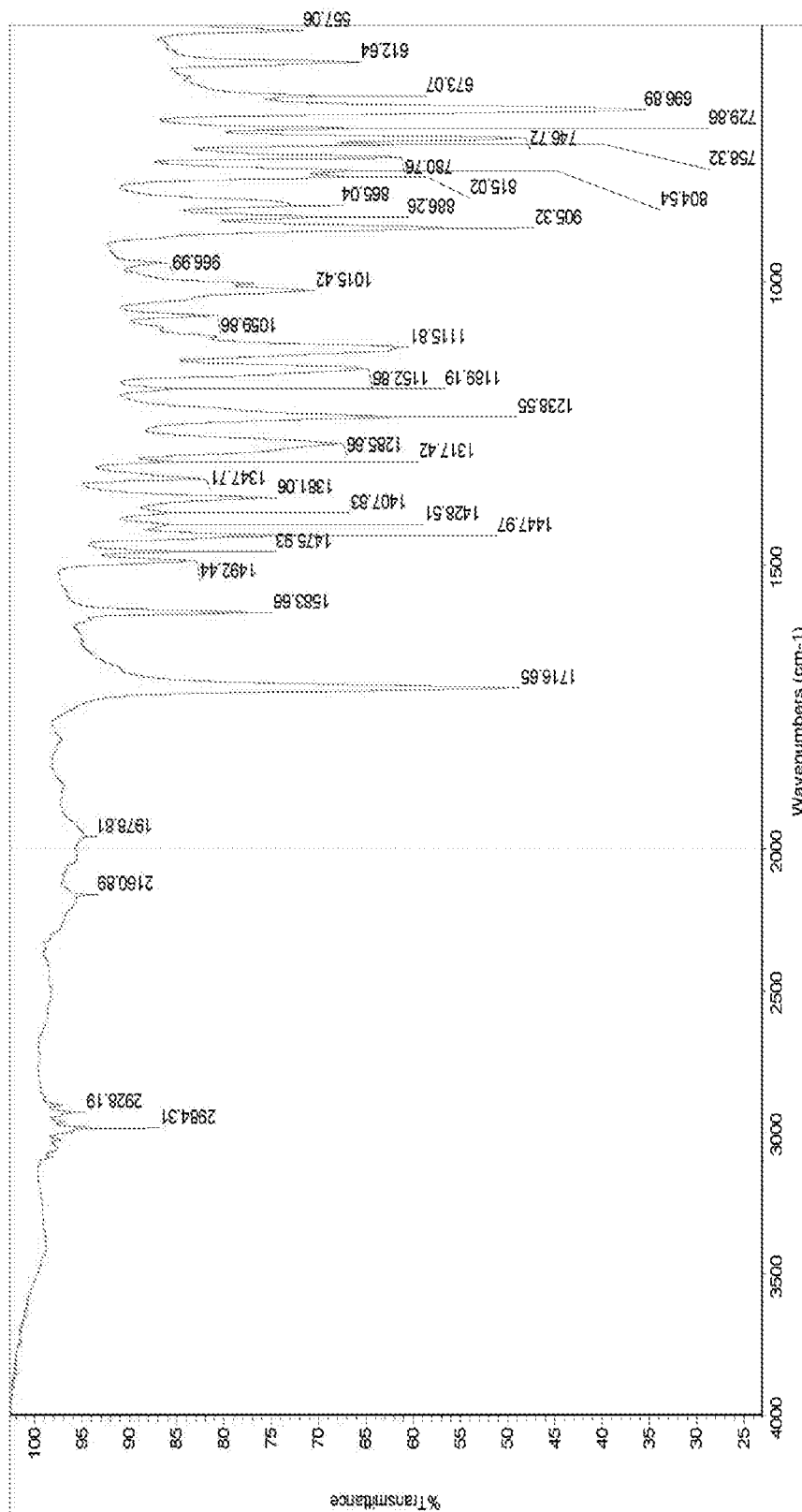


Figure 1

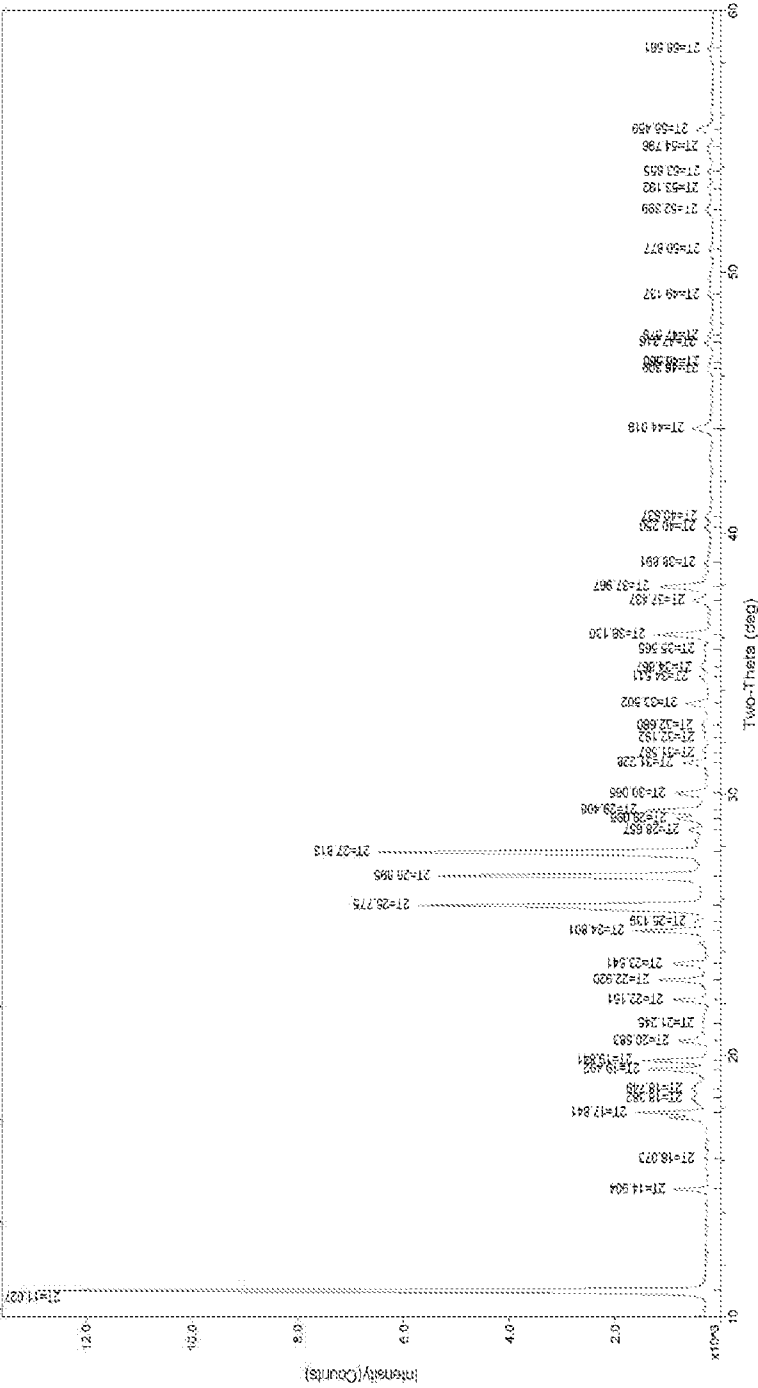
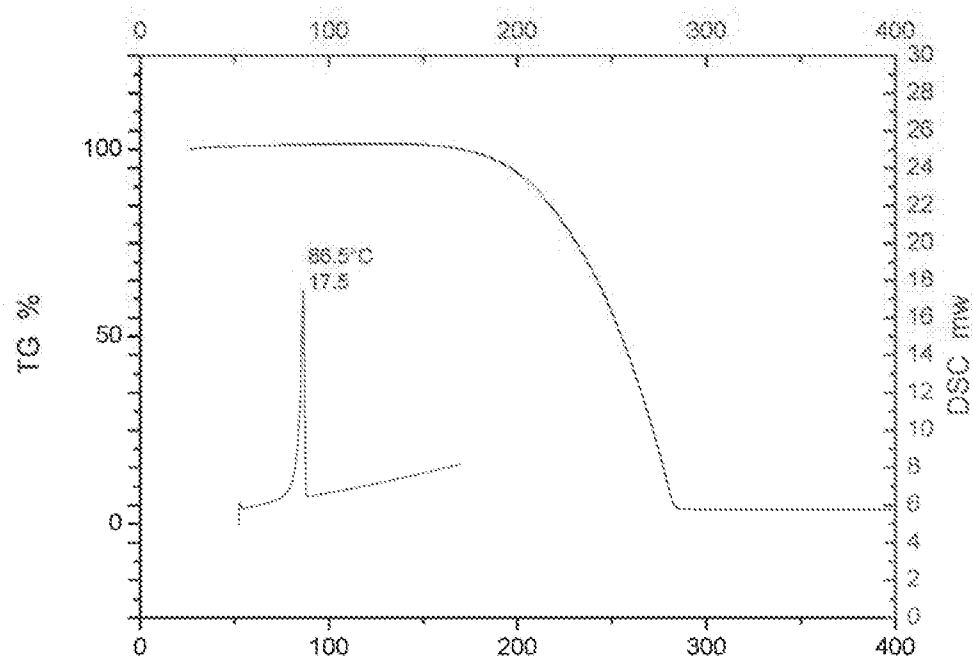


Figure 2

**Figure 3**

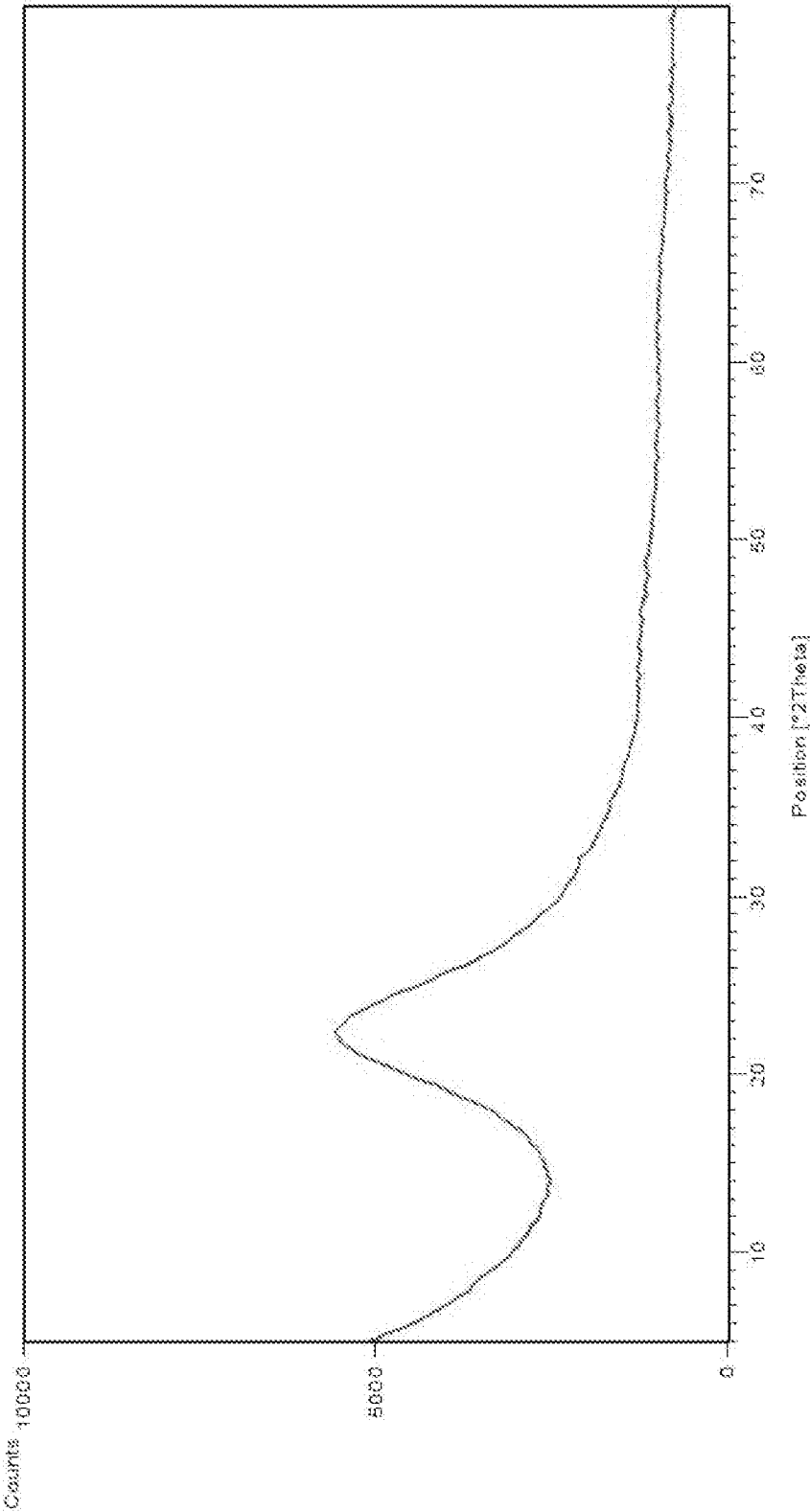


Figure 4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2016/098343

A. CLASSIFICATION OF SUBJECT MATTER

C07D 261/04(2006.01)i

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)

C07D 261/-

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)

EPODOC;WPI;CNTXT;USTXT;Web of science;Registry(STN);Caplus(STN);rotam agrochem, isoxadifen, ethyl, dihydro, diphenyl, isoxazolecarboxylic, acid, crystal, 163520-33-0

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 103172582 A (JIANGSU AGROCHEM LAB CO. LTD., JIANGSU INST ECOMONES CO. LTD.) 26 June 2013 (2013-06-26) example 1	1-23
X	JING, Lei et al. "Process Improvement on the Synthesis of Isoxadifen-ethyl" <i>Chinese Journal of Synthetic Chemistry</i> , Vol. 23, No. 7, 31 July 2015 (2015-07-31), pages:630-632	1-23
X	CHANG, Peng et al. "Synthesis of Isoxadifen-ethyl as Herbicide Safener" <i>FINE CHEMICAL INTERMEDIATES</i> , Vol. 44, No. 2, 30 April 2014 (2014-04-30), pages:21-24	1-23
X	WANG, Hui et al. "Synthesis of Isoxadifen-ethyl Safener" <i>AGROCHEMICALS</i> , Vol. 51, No. 11, 30 November 2012 (2012-11-30), pages:792-793, 810	1-23

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 November 2016

Date of mailing of the international search report

09 December 2016

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2016/098343

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	103172582	A	26 June 2013	CN	103172582	B	08 April 2015