(54) Title: SYNTHESIS AND USE OF IMPROVED POLYOL ESTER INSECTICIDES

(57) Abstract: The present invention relates to an environmentally acceptable synthesis method of polyol esters that produces no toxic by-products methods during the synthesis. The present invention also provides for the use of these esters as safe effective insecticides. The present invention discloses that sorbitol decanoate is a marginally more effective insecticide against the two-spotted spider mite than other esters, including the sucrose octanoate, which is demonstrated in.
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SYNTHESIS AND USE OF IMPROVED POLYOL ESTER INSECTICIDES

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99-33610-7466 awarded by U. S. Department of Agriculture.

FIELD OF THE INVENTION
The present invention relates to methods of synthesis of polyol ester insecticides. More
particularly, this invention concerns a synthesis method for sugar esters which ensures that the
resulting chemical composition and structure of the sugar esters have insecticidal activity.

BACKGROUND OF THE INVENTION
Sucrose octanoate has proven to be a useful insecticide compound. Varieties of sucrose esters
are contained in the natural wax of leaves. Discussions of these esters may be found, for example, in
contained in the mixture of sucrose esters made when coconut fatty acids are used to make sucrose
esters. These sucrose esters are readily biodegradable and hydrolyze to readily metabolizable sucrose
and fatty acid. Sucrose esters can be made by the methods disclosed in U.S. Patent 5,756,716,
Other methods for making these sugar ester compounds are also known and referenced in this patent.

The efficient production of sucrose octanoate involves several steps, including an esterification, a
transesterification and then a purification step. It would be extremely useful to have compounds with
similar insecticidal activity, similar environmental acceptability, made from similar natural products,
that could be synthesized in fewer steps. Unfortunately there is no means of predicting the chemical
structures that will have insecticidal activity. There is no general agreement as to the mechanism of
the sugar ester compounds’ insecticidal activity.

One hypothesis is that the compounds like sucrose laurate or sucrose octanoate act as surfactants to
dewax the insect’s protective coating. The insect then either dehydrates or is readily attacked by ever
present environmental microbes. This hypothesis is supported by the observation that the compounds
are “contact” insecticides. Since the sucrose esters are constituents of plant leaves, there is another
hypothesis that the compounds somehow interfere with the metabolism of the insect to prevent them from eating the tissue that the esters protect. This hypothesis requires ingestion of the material by the insect and cannot be ruled out since “contact” can also result in ingestion by the insect when the insect is feeding on the treated material.

It is also known that the short chain sucrose esters that are effective as insecticides have certain properties that seem to enhance that activity. Chortyk and co-workers at the United States Department of Agriculture [see Chortyk, O.T., Pomonis, J.G., and Johnson, A.W., J. Agric. Food Chem., 44, 1551-1557 (1996)] concluded that the sucrose esters with fatty acid chain lengths below 12 were more effective especially when there were 2 or 3 side chains on the sucrose. The fact that there are eight hydroxyl groups that can be esterified in sucrose means that, in principal, one can make 8 sucrose monoester, 28 diester and 56 triester isomers. It is unpredictable and, moreover, it is not known if all esters of one type (e.g. all monoesters, all diesters, etc.) are equally effective. Molecular orbital calculations performed in the inventors’ laboratory suggest that not all esters are equally likely to be produced during synthesis.

SUMMARY OF THE INVENTION

In one aspect the present invention relates to a novel and new environmentally friendly method of synthesis of various polyol esters. The inventors found that the synthesis method is critical in defining the distribution of isomers in complex molecules with the subsequent result that one must either specify the exact method of synthesis as a mean of selecting the resultant isomers that function as effective and environmentally safe insecticides and/or the exact ratios of the isomers involved.

More particularly another aspect of this instant invention is the use of the inventors’ synthesis selected isomeric esters as safe effective insecticides. The inventors found the surprising and unexpected result that octanoic acid (C8) sorbitol esters are more effective as insecticides, and that the decanoic acid (C10) acid esters are the most effective insecticides for the xylitol esters.

Also there was an unexpected finding that for sucrose octanoate the monoesters were more effective as insecticides than either the diesters, trimesters, or mixtures thereof. This finding is in contradiction to the finding of Chortyk who concluded that sucrose esters with fatty acid chain lengths below 12 were more effective especially when there were 2 or 3 side chains on the sucrose. Additionally Chortyk synthesized his esters through the use of a multi-step process using acid chlorides which generated hazardous by-products. His method of synthesis generated primarily diesters and triesters while the method of U.S. Patent 5,756,716 optimally can generate a high percentage of monoesters.
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DETAILED DESCRIPTION OF THE INVENTION

The method of preparation of the polyl esters, in particular those of sorbitol and xylitol, of this invention is best explained in terms of seven steps. One of the objects of the preparation method is to have an environmentally acceptable synthesis that generates essentially no toxic by-products. Another object is to develop a concise method that allows the entire range of esters to be prepared using essentially the same procedure thus allowing either mixed esters to be produced or the same production facility to be used to make a range of esters that could be targeted against specific insects. Without limiting the scope of this invention as expressed by the claims which follow, the synthesis steps will be discussed briefly.

The process of preparation of the polyl esters is basically as follows:

1. The desired organic acid (e.g. octanoic, deconoic, but not limited to these) is charged to the reactor at a temperature sufficiently high to keep the selected acid in liquid form.

2. The polyl (e.g. either xylitol or sorbitol, but not limited to these) is added in an amount that would drive the production of the monoester stoichiometrically plus an additional 10% to ensure the reaction is driven essentially to completion.

3. An esterification catalyst is added. Any esterification catalyst can normally be used such as sulfuric acid or phosphoric acid. In the preferred embodiment phosphoric acid is the esterification catalysts as neutralization at the completion of the reaction provides a phosphate salt that can either remain in the product (since phosphorus is an essential plant nutrient and phosphates are a known method of providing phosphorus to biological plants) or removed by filtration if so desired providing a separate stream whereupon the phosphorus salt can be sold separately for use in fertilizer.

4. The reactor is held at a temperature sufficiently high along with a pressure sufficiently low to allow water to be removed as the esterification reaction proceeds to completion. For most of the esters a temperature around 150°C and atmospheric pressure was used but, the reactor is not limited to these temperature and pressure parameters.

5. The reaction is allowed to proceed until the remaining organic acid reaches a low equilibrium value. This point can be determined very simply by monitoring the free acid content of the reaction mixture and comparing differing reaction times (see Example 1 and 2). When the free organic acid is no longer reduced the reaction is essentially completed. The equilibrium value in weight percent depends on the molecular weight of the organic acid and the structure of the isomers formed. Once determined for a particular organic acid and polyl combination, the weight percent equilibrium value can then be used as a measure of reaction completion.

6. At the completion of the reaction (approximately 18-30 hours for the esters synthesized for the insecticidal studies) the solution is neutralized with an amount of base that is sufficient to
neutralize all of the mineral acid that was used as a catalyst plus bring the resultant solution to a desired pH for subsequent use. If calcium hydroxide is used as the base, calcium phosphate can be filtered out of the product. Other bases could be used depending on the desired nature of the final product. This procedure was followed to allow for a product that exhibited good water solubility with little or no residual fine solid particles.

7. The product (filtrate from Step 6) is analyzed and is ready for use.

This procedure of this present invention is deliberately made deceptively simple. Due to the fact that the insecticide nature as well as other properties of these materials change depending on the isomers produced during the reaction, it is necessary to have a simple process that can be repeated with little difficulty. The only "waste product" of the reaction is the water removed during the esterification. The equipment and reaction conditions are selected in such a manner that the tendency of any of the organic acid to distill over with the water is thwarted by the use of appropriate reflux allowing the water to be removed and the acid to fall back into the reactor. Thus, in a preferred embodiment a distillation column (tray or packed column) is used over the reactor to insure retention of the acids.

Sucrose octanoate is synthesized by the method described in U.S. Patent 5,756,716, incorporated herein by reference. The resultant product, sucrose octanoate, is found to have monoesters that are more effective as insecticides than the diesters and triesters of sucrose octanoate. Figure 1 shows the results on pear psylla for the sucrose octanoate with high monoester content prepared by the referenced method as compared to the Chortyk esters, which is comprised of high di- and triesters. This unexpected and surprising finding is in contradiction to the earlier finding of Chortyk. The inventors of the above described process find the method of synthesis is critical in defining the distribution of isomers in complex molecules with the subsequent result that one must either specify the method of synthesis and/or the exact nature of the isomers involved as a mean of selecting the best insecticides.

To study the chemical differences between the sucrose octanoate synthesized by Chortyk and the inventors' material, the products were subjected to thin layer chromatography under identical conditions, side by side, on the same plate. The chromatograms obtained by digitization of the plates are shown in Figures 2-4. A chromatogram of a commercial sucrose stearate product, obtained by the same method, is shown in Figure 5. Although the commercially available sucrose stearate product shown in Figure 5 does not have insecticidal activity, it is shown as an independent example of the nature of a product that is primarily a monoester. In this analytical methodology the higher the number of free hydroxyl groups in the molecule the tighter it is bound to the silica substrate. Thus monoesters move more slowly and appear nearer the origin on the chromatogram while the diesters
move fast and the triesters faster; thus the di- and triesters appear further from the origin on the chromatogram. The result is separation of the various isomer fractions.

Figure 2 shows a chromatogram of the esters made by Chortyk. Note that there are many peaks resulting from the higher isomers (di- and trimers). Figures 3 and 4 show two different batches of sucrose octanoate made by the method of U.S. 5,756,716. There are fewer peaks with lesser area than the same sucrose octanoate ester made by the acid chloride route. The commercially available product is shown in Figure 5. The sucrose octanoate made by the procedure of this instant invention and having a monoester content of about 80% or greater was found to be more effective as an insecticide.

The thin layer chromatography technique is very reproducible as to the extent and number of “bands” that characterize the different isomers within the product. If liquid chromatography is utilized, the individual isomer “peaks” tend to merge and overlap making resolution difficult. With the advent of computer scanners to convert the chromatogram into digital form, the thin layer technique rivals or exceeds liquid chromatographic techniques. The use of computer digitization is an improvement on the densitometry techniques previously used with thin layer and gel chromatography.

In the sucrose studies the octanoate ester was found to be the approximately optimal chain length. Octanoic acid is a reasonably abundant fatty acid fraction of natural oils (e.g. coconut oil) after the oil is “split”, i.e. hydrolyzed to glycerol and fatty acids. Nature prefers even chain fatty acids. The odd chain fatty acids are also likely to be reasonably effective as insecticides; however, it is the inventors’ purpose to make the biodegradation products resulting from the insecticides as natural as possible. It is well known that the long chain fatty acid esters of sucrose (e.g. sucrose stearate) are extremely mild materials with excellent surfactant properties. These long chain fatty acid esters of sucrose have been used as food emulsifiers for many years.

Finding useful analogs of sucrose octanoate is a matter of experimental invention. The chemical structure can be suggestive, however. The objective was to find materials that:

1. Are simpler to synthesize
2. Would have environmental fates similar to sugar and fatty acid esters
3. Would have similar insecticidal activity when used either alone or in combination

A wide variety of compounds were synthesized. The compounds that were proven to have the best activity when compared to sucrose octanoate are sorbitol and xylitol esters of short chain fatty acids, particularly the octanoic and decanoic acid monoesters. These compounds were found to be easier to
prepare than the sucrose octanoate. They can be synthesized directly from the raw materials in a single step using only a neutralizable mineral acid as a catalyst in the process described earlier. Due to the greater ease of synthesis these materials could be less expensive even if they are slightly less effective than sucrose octanoate as an insecticide.

Surprisingly and unexpectedly, there is no one chemical structure that was shown to be optimally effective for all the insects tested for the sorbitol and xylitol esters. This differs from the sucrose esters where the inventors found that not only is the octanoate the most effective but the distribution of isomers toward the monoesters also defines a superior insecticide. It was found that the optimum chain length for the other sugar esters differs depending on the insect species. This finding seems to support a mechanism wherein the compound is not directly toxic but rather matches some property of the insect’s covering materials, i.e., this unexpected and surprising finding provides support for the “dewaxing” hypothesis, wherein “dewaxing” refers to the destruction of the insect’s protective coating. The differing chemical make-up of the insect and its covering materials would be optimally matched to different “solvent” compounds, wherein the isomer distribution of the compound would be optimized to the individual insect species.

Table 1 provides a listing of the compounds of interest. Five of them have been reported at sometime in the past and have been assigned Chemical Abstract Service (CAS) Registry numbers while three appear to be new to the literature since no CAS registry number was found.

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<td>Xylitol dodecanoate</td>
<td>Xylitol laurate</td>
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The chain lengths were systematically varied to determine if the chain length was critical as to the effectiveness of each compound as insecticides. The compounds were tested against pear psylla, tobacco hornworms, tobacco aphids and two-spotted spider mites.
Figure 6 shows the kill data for the sorbitol esters on pear psylla. It is clear that the C8 chain length acid version is the most effective. For the xylitol data in Figure 7, however, it appears that the C10 chain length acid ester is the most effective. This is a very surprising and unexpected result because the shift in the size of the hydrophobic portion of the molecule for the xylitol esters has not kept pace with the shift in the size of the hydrophilic portion of the molecule.

If the activity was explained by a simple surfactant picture, one would expect that a certain hydrophilic-lipophile balance (HLB) would hold. When the size of the hydrophile decreases as it has in going from sorbitol to xylitol one would expect the size of the lipophile to also decrease to maintain the same HLB relationship. The determination of the HLB for a molecule that is effective allows one to utilize other compounds with substantially similar HLB’s. The series of synthesized compounds in this instant invention do not evidence this behavior, and thus the compounds that are effective are not obvious and are not predictable. A discussion of the relationship of the molecular structure to the HLB is given by Arthur W. Adamson, "Physical Chemistry of Surfaces", Third Edition, John Wiley, 1976, pp. 505-507.

Figure 8 shows the effectiveness of sucrose octanoate made by the methods of U.S. 5,756,716 against tobacco aphid. Figure 9 shows that sorbitol octanoate is more effective than sorbitol decanoate against tobacco aphid. Note that sorbitol decanoate could still be a commercially viable product if the cost of decanoic acid was less than octanoic acid by an amount that would compensate for the increased use needed to maintain equal effectiveness. The simplicity of the method of preparation of the sorbitol and xylitol esters and the fact that the method is essentially the same for all of the sorbitol and xylitol esters makes the economic choice essentially only dependant upon the raw material costs.

Figure 10 shows that xylitol laurate is more effective than xylitol decanoate against the tobacco aphid. This was unexpected and in contrast to the case with pear psylla where the decanoate was most effective.

Figure 11 shows that sorbitol decanoate is more effective than xylitol laurate against the tobacco aphid. Of greater importance, however, is the fact that both of these materials are better than a commercially available insecticidal soap product (M-Pede, Mycogen Corp., San Diego, CA). Figure 12 compares several of these materials for use against the two-spotted spider mite and in this case the sorbitol decanoate is marginally more effective than the others including the sucrose octanoate.

The following examples of making polyol esters are presented for purpose of elucidation, and not limitation, of the present invention. While specific acids and sugars are disclosed herein, those of
ordinary skill in the art would be able to make minor modifications while achieving the same or substantially similar results. It is intended that equivalent polyl esters fall within the scope of any claims appended hereto. Other polyl esters as discussed above may also be made using the process of this invention.

Examples 1 and 2 were run to compare different reaction times for the degree of conversion. This type of benchmark reaction can be performed to determine optimal conditions for other polyl esters.

Example 1

Preparation of sorbitol octanoate: 432.44 grams of octanoic acid was put into a 2-liter round bottom, three-neck flask with a short distillation head. A mechanical stirrer was connected and 598.51 grams of sorbitol was slowly added. The catalyst in the reaction was phosphoric acid and 30.93 grams were added. A temperature controller and heating mantle were attached and the temperature of the reaction was set at 150°C. The reaction was stopped after 21 hours. The phosphoric was neutralized with 26.02 grams of calcium hydroxide. The solution was filtered to remove the calcium phosphate precipitate. The density of the product was 1.4 g/cc and the free acid was 6.40%. The degree of reaction completion was thus about 85.5%

Example 2

Preparation of sorbitol octanoate: 438.52 grams of octanoic acid, 600.10 grams of sorbitol and 32.122 grams of phosphoric acid was placed into a round bottom flask with a mechanical stirrer and short distillation head attached. The temperature was set at 150°C. The reaction proceeded until the free acid value was 3.88%. Total reaction time was 28 hours. The phosphoric acid was neutralized with 27.015 grams of calcium hydroxide. The product was analyzed and the density was 1.4 g/cc and the ash was 2.33%. The degree of reaction is thus 91.3%

Example 3

Preparation of xylitol octanoate: 417.0 grams of octanoic acid was poured into a 2-liter round bottom flask with a short distillation head. A mechanical stirrer and short distillation head were attached and a heating mantle and a temperature controller was used to maintain temperature at approximately 150°C. 462.48 grams of xylitol was added slowly along with 32.422 grams of 75% phosphoric acid.
Example 4

Sorbitol caproate was prepared by adding 348.48 grams of caproic acid and 546.51 grams of sorbitol to a 2-liter round bottom flask with a mechanical stirrer, heating mantle and temperature controller. Phosphoric acid was used as the catalyst and 39.12 grams of 75% phosphoric acid was added to the reaction. The temperature was set for 150°C and the pressure was atmospheric pressure. The total reaction time was 24 hours. After 24 hours the phosphoric acid was neutralized with 32.90 grams of calcium hydroxide. The solution was filtered to remove the calcium phosphate precipitate. The final product was analyzed and the free acid remaining in the product was 3.97%, the density was 1.8 g/cc and the ash value was 1.42%. The degree of reaction completion was thus 89.3%.

Example 5

Sorbitol decanoate was prepared by adding 380.80 grams of sorbitol and 302.0 grams of decanoic acid to a one-liter round bottom flask. 27.14 grams of 75% phosphoric acid were added. The agitator was turned on and the temperature was set to 150°C. The total reaction time was seven hours and ten minutes. The phosphoric acid was neutralized with 22.83 grams of calcium hydroxide and the solution was filtered to remove the calcium phosphate. The final product was analyzed and the free acid remaining was 7.50%. The density was 1.05 g/cc and the ash value was 1.00%. The degree of reaction completion was thus 76.0%.

Example 6

Xylitol laurate was prepared by adding 466.8 grams of xylitol to 420.0 grams of lauric acid in a two liter round bottom flask. A mechanical stirrer, heating mantle and temperature controller were attached. Phosphoric acid was used as the catalyst and 35.25 grams of 75% acid was added. The temperature was set to 150°C and the total reaction time was nine hours. At the end of nine hours the phosphoric acid was neutralized with 29.65 grams of calcium hydroxide and the solution was filtered to remove the calcium phosphate that formed upon neutralization. The xylitol laurate was analyzed and had 11.0% free acid remaining and the ash value was only 0.60%. The degree of reaction completion was thus 77.5%.

Example 7
Sorbitol laurate was prepared in a similar manner as xylitol laurate. In this case, 600.76 grams of lauric acid and 776.01 grams of sorbitol were added to a round bottom flask. Phosphoric acid was used as the catalyst and 54.73 grams of 75% acid was added. A mechanical stirrer was used to provide the agitation and a heating mantle and temperature controller were used to control the temperature. The temperature of the reaction was set at 160°C. The reaction was stopped after 29.5 hours and the free fatty acid was high at 12.0%. The solution was neutralized with calcium hydroxide and filtered to remove the calcium phosphate precipitate. No other analysis was done on this product. The degree of reaction completion was thus 73.2%.

Example 8

Xylitol decanoate was prepared. 602.5 grams of xylitol were placed in a two liter round bottom flask with a mechanical stirrer and heating mantle and temperature controller attached. 517.08 grams of decanoic acid were added to the flask. Phosphoric acid was used as the catalyst and 44.52 grams of 75% phosphoric acid was added. The reaction proceeded for 13 hours and 30 minutes. At the end of the reaction the phosphoric acid was neutralized with calcium hydroxide and the solution was filtered to remove the calcium phosphate precipitates. The free acid was measured and the value was 6.9%. The degree of reaction completion was thus 85.7%.
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CLAIMS:

We claim:

1. A method of synthesis of effective insecticides comprising:
   (a) selecting an organic acid with six to twelve carbons;
   (b) selecting a polyol with five or six carbons;
   (c) charging a reactor with said organic acid at a temperature to keep said acid liquid;
   (d) adding said polyol in a quantity that produces a monoester stoichiometrically plus approximately an additional 10%;
   (e) adding an esterification catalyst;
   (f) maintaining said temperature and pressure in said reactor to remove water until reaction is essentially complete;
   (g) neutralizing solution with a base and bringing said solution to desired pH; and
   (h) filtering said solution to remove solid particles.

2. A method of synthesis as in Claim 1 where the preferred embodiment uses a distillation column over said reactor to retain said acids in reaction mixture.

3. A method of synthesis as in Claim 1 wherein the organic acid is selected from the group consisting of octanoic acid, decanoic acid, caproic acid, and lauric acid.

4. A method of synthesis as in Claim 1 wherein the polyol is xylitol or sorbitol and the esterification catalyst is phosphoric acid or sulfuric acid.

5. A method of synthesis as in Claim 2 or 3 wherein said temperature is between 140° C and 175° C and said pressure is atmospheric.

6. The method of claim 1 wherein said monoester is sorbitol octanoate.

7. The method of claim 1 wherein said monoester is sorbitol decanoate.

8. The method of claim 1 wherein said monoester is xylitol decanoate.

9. The method of claim 1 wherein said monoester is xylitol laurate.

10. A method for treating plants to reduce or eliminate insect pests utilizing monoesters with chemical ratios and compositions as synthesized in claim 1, comprising the steps of:
    (a) mixing said monoesters in water such that concentration of said monoesters is 0.05% to 3.0%; and
    (b) spraying foliage infested with said insect pests at intervals to keep said insect pests reduced.

11. A method for treating plants to reduce or eliminate insect pests utilizing monoester of sucrose octanoate of high monoester content comprising the steps of:
    (a) mixing said monoesters in water such that concentration of said monoesters is 0.05% to 3.0%; and
    (b) spraying foliage infested with said insect pests at intervals to keep said insect pests
12. The method of claim 11 wherein the monoester concentration of sucrose octanoate is 80% or greater.

13. A method for treating plants to reduce or eliminate insect pests utilizing monoesters of five or six carbon sugars or reduced sugars and organic acids with six to twelve carbons comprising the steps of:
   (a) mixing said monoesters in water such that concentration of said monoesters is 0.05% to 3.0%; and
   (b) spraying foliage infested with said insect pests at intervals to keep said insect pests reduced.

14. The method of claim 13 wherein the monoester is sorbitol octanoate.

15. The method of claim 13 wherein the monoester is sorbitol decanoate.

16. The method of claim 13 wherein the monoester is xylitol decanoate.

17. The method of claim 13 wherein the monoester is xylitol laurate.


Figure 1

Sucrose Octanoate Isomers

Concentration (wt %)

Pear Psylla Kill in 15 min. (%)
Relative Intensity

Retention Time

Sucrose Octanoate from Acid Chlorides

Figure 2
Relative Intensity

Retention Time

Sucrose Octanoate from US 5,756,716

Sample 1

Figure 3
Figure 4
Sample 2
Sucrose Octanoate from US 5,756,716
Figure 5

Commercial Sucrose Stearate 55% Monoster
Figure 6

Percent Kill of Pear Psylla in 15 minutes

Concentration in Solution (% by weight)

Percent Kill

C6
C8
C10

sorbitol esters

SUBSTITUTE SHEET (RULE 26)
Percent Kill

Concentration in Solution (% by weight)

Percent Kill of Pear Psylla in 15 minutes

Figure 7

xylitol esters

C8 → C10 → C12
Percent Kill

Concentration (weight %)

Percent Kill of Tobacco Aphid in 15 Minutes

Figure 10

Substitute Sheet (Rule 26)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC(7) : C07C 31/18
   US CL. : 568/852, 853

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)
   U.S. : 568/852, 853

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)
   EAST, STN - FILES REGISTRY, MEDLINE, BIOSIS, BIOTECHNO, CAPLUS, EMBASE, JICST, WPIDS

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>
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<td>US 4,623,540 A (COSTANZA ET AL) 18 November 1986 (18.11.1986), column 5, 3rd paragraph.</td>
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<td>GB 2,119,251 A (FISON PLC) 16 November 1983 (16.11.1983), page 1, 2nd paragraph.</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: 31 October 2001 (31.10.2001)

Date of mailing of the international search report: 19 DEC 2001

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