**Patent law, 5727 – 1967** (patent law)

**Before the honorable Commissioner of Patents, Designs and Trademarks**

**Re**: **Patent request #221005** (**the** **petition**)

Presented by **FINCHIMICA S.P.A.** (**the** **petitioner**)

Represented by Liad Whatstein & Co.

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**About**: **Opposition to a patent application on request** (**opposition**)

 Filed by **Adama Machteshim LTD**.

 Represented by Gilat Barkat and Co. (**the respondent**)

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**Expert opinion**

I, the undersigned, associate professor Yoav Ishan, I.D. number 057170219, residing at Avigayil Street 20 Haifa Israel, was asked by the counsel for the respondent, the law firm of Gilat Barkat and Company, to give my opinion on behalf of **Adama Machteshim LTD** (**Adama** or **opposition**), as part of the opposition that Adama filed against the Israeli patent application number 221005 (**patent application or application**) filed by **FINCHIMICA S.P.A.** (the **petitioner**).

 The counsel for the respondent explained to me that the patent application is claiming priority on the basis of an Italian patent application BS2010A000118 dated July 7th 2010 (**the** **priority date**).

I am giving my expert opinion in lieu of testifying in court and I hereby claim that I fully understand that as far as the penal code for giving false testimony under oath is concerned, this expert opinion with my signature is equivalent to giving a sworn testimony before the honorable Commissioner of Patents.

 **a**. **Education and academic background, expertise and experience**

1. In 1993 I was awarded a PhD from the Hebrew University, Jerusalem on my research in the field of chemistry. Currently, I am an associate professor in the Shulich Faculty of Chemistry at the Technion, Israel Institute of Technology.
2. My expertise in the field of chemistry is expressed and documented in my many publications that deal with among other topics in the field of organic chemistry. Throughout the years, I took part in many research projects and I published over 95 scientific articles in many world renowned professional scientific journals in the fields of chemistry and material sciences. In addition, I published chapters in patents and article compendiums. All this is detailed in my CV which is attached to this document as **appendix a**.
3. In addition to my academic duties, I initiated and founded a company based on innovations that I played a part in their development. I am a director in that company from its founding in 2003, I was in charge of development for a few years and I am currently an advisor for the company in the field of chemistry.
4. It is in my opinion, that my education, academic experience, the list of publications that I took part in their writing and the additional information that is detailed in my CV that is attached to this expert opinion, gives me the authority to give this expert opinion.

**b. Material that I scanned and the scope of my opinion**

1. For this expert opinion, I reviewed the patent application, the written arguments opposing and written response by the petitioner (including the appendixes). In addition, I reviewed addition relevant material as detailed below.
2. A list of the publications that I used to give my expert opinion is summarized in the table below (for convenience sake, the appendices are marked as in the opposing written arguments). The list of documents is attached to this expert opinion and is marked as **appendix b**.
3. It should be noted that all emphases in the quoted various publications were done by the undersigned unless otherwise stated.

|  |  |  |
| --- | --- | --- |
| **Appendix** | **Publication** | **Publication identification** |
| [4] | **AU 2010100462** A4 (Australian Patent) to Gharda, published on June 17, 2010  | **462** |
| [5] | **US 3,928,372** published on December 23, 1975 | **372** |
| [6] | **WO 01/30760** (PCT International Application Publication) (Clavel *et al*.)Published on May 3, 2001.  | **760** |
| [7] | **US 6,013,761** to Zierer et al. Published on January 11, 2000 | **761** |
| [8] | **WO 2007/122440** to Gharda et al. published on November 1st 2007. | **440** |
| [9] | **US 2,813,896** to Krimm et al. Published on November 19, 1957.  | **896** |
| [10] | **Kaczorowska et al**.,”Oxidation of Sulfides to Sulfoxides. Part 2: Oxidation by Hydrgen Peroxide,” Tetrahedron, 61: 8315-8327 (2005). | **Kaczorowska** |
| [11] | Chapter 7 of ***Modern Oxidation Methods***, J.E. Backvall, ed., WILEY-VCHVerlag GmbH & Co. KGaA (2004) | **Modern Oxidation Methods** |
| [12] | **Swern**, D. “Organic Peracids,” Chem. Rev., 1949, 45 (1), pp 1–68 | **Swern** |
| [13] | **Golchoubian et al**.,”Effective Oxidation of Sulfides to Sulfoxides with Hydrogen Peroxide under Transition-Metal-Free Conditions” Molecules 2007, 12, 304-311 | **Golchoubian** |
| [14] | **Uemura**, Sakae; 6.2 Oxidation of Sulfur, Selenium and Tellurium ; Kyoto University, Japan, vol. 7, Ley. S..V. Ed.; Pergman: Oxford, 1991, 757-787. | **Uemura** |
| [15] | Frank P. **Greenspan**, "The Convenient Preparation of Per-acids", *J. Am. Chem. Soc.*, 1946, *68* (5), pp 907–907 | **Greenspan** |
| [16] | **Hussain**, S.; Bharadwaj, S. K.; Pandey, R.; Chaudhuri, M. K. Eur. J. Org. Chem2009, 20, 3322–3319 .  | **Hussain** |
| [17] | Alexander **Treiber**, J. Org. Chem. 2002, 67, 7261-7266. | **Treiber** |
| [18] | Clifford G. **Venier**, Thomas G. Squires, Yu Ying Chen, Barbara F. Smith, "Peroxytrifluoroacetic acid oxidation of sulfides to sulfoxides and sulfones", J. Org. Chem. 1982, 47, 3773-3774 | **Venier** |
| [19] | EP 2 035 390 B1 | **390** |
| [20] | Samples of search results from 'Scifinder'  | **Scifinder** |
| [21] | Slides from course in organic chemistry  | **Slides Chemistry** |
| [22] | **March**’s Advanced Organic Chemistry Reactions, mechanisms, and structure, 6th edition, M.B. Smith, J. March Wiley-Interscience, 2007, pp.1780-1783 | **March** |
| [23] | M. **Pandeeswaran,** Kinetics and mechanism of the oxidation of methionine by quinolinium chlorochromate, J Serb. Chem. Soc. 70 (2) 145–151 (2005) | **Pandeeswaran** |
| [24] | Fu-Lian **Hsu**, Oxidation of 2-Chloroethyl Sulfides to Sulfoxides by Dimethyl Sulfoxide,J. Org. Chem. 1990,55, 4153-4155 | **Hsu** |
| [25] | Scott **Searles**, Jr., Oxidation of Organic Sulfides with Dimethyl Sulfoxide, Journal of Organic Chemistry, 23, 2028-2029; 1958 | **Searles** |

**c. The questions that I was requested to answer**

1. I was asked by the opposition to give an opinion to the following questions:

8.1 What is the invention that is claimed in the patent application?

8.2 Was the claimed invention in the patent application novel at the priority date?

8.3 At the priority date, was the invention claimed in the patent application obvious to someone skilled in the arts?

1. Before I answer these questions, I would like to give some relevant background so as to better understand the invention and the prior knowledge in this field.

**D. The background for the invention**

 **D.1. General background**

1. The various derivatives of the 1-phenyl pyrazole family (see figure 1 right figure), for example Fipronil (Figure 1 left figure), were found to be effective broad range insecticides for use in agriculture. Studies have shown that Fipronil targets and damages the insect’s central nervous system and is therefore an effective insecticide against cockroaches, flies, wasps, ants and other insects and is also effective in curbing agricultural pest populations.

 

 **Figure 1.**

1. One of the ways to produce Fipronil includes at the last step, selectively oxidizing a sulfur atom in a sulfide group to produce a sulfoxide[[1]](#footnote-1), as seen in Figure 2. The two red squares in the figure define the chemical reaction site where the sulfide group in molecule 3 changes to a sulfoxide in molecule 1, whereas in the other parts of the molecule there are no chemical changes.

 

 **Figure 2**

A possible way to prepare Fipronil, 1, from its source molecule, 3, using a selective oxidation step of the sulfide group of 3 to a sulfoxide group in the product 1.

1. Selectivity in the oxidation process means that a specific functional group in the reactant, in our case a sulfide group, oxidizes a specific group in the wanted product, in our case, a sulfoxide group without an oxidation reaction or any other competing reaction occurring in any other functional group in the reactant or the product which will cause a significant loss in the process’s yield (for instance, assuring that the sulfoxide group in the product does not continue to oxidatively react to become a sulfone, as clarified below).
2. In the process claimed in the patent application, the oxidized compound (source material) is a member of the family of compounds with a general formula of **II**, as seen in Figure 3 (**source material II/ compound II/ formula II**); in which R1 and R2 are independently hydrogen and halogen atoms.
3. According to the method in the patent application, the sulfur atom (S, marked with a red arrow in **Figure 3**) of compound **II** is the focal point of the selective oxidation in a process in which the sulfide group becomes a sulfoxide (as marked with the red arrow in **Figure** **4**), and in this manner compound **II** is changed to compound **I**, whose general structure is shown in **Figure 4** (**material I/ compound I/ formula I**); in which R1 and R2 are independently hydrogen and halogen atoms.

 

 **Figure 3**

The general structure of compound family **II** in which R1 and R2 are independently hydrogen and halogen atoms. The oxidized atom is marked with a red arrow.

 

 **Figure 4**

The general structure of compound family **I** in which R1 and R2 are independently hydrogen and halogen atoms. The oxidized atom is marked with a red arrow.

1. As stated above, the described process that is claimed in patent application is a selective oxidation process of a family of compounds to achieve a family of wanted products. Below, I will detail the prior basic knowledge that someone skilled in the arts knew at the priority date, in regards to oxidation reactions in general, regarding oxidizing sulfides to sulfoxides and regarding oxidation reactions of the family of compounds **II** or their analogues to the compound family **I** or their analogues.

 **d.2. Oxidation reactions**

1. Oxidation reactions of a given compound is defined as a process in which one or more of the following events take place[[2]](#footnote-2): (1) The compound loses one or more electrons; (2) one or more atoms of the compound has an increased oxidation state; (3) the molecule acquires one or more oxygen atoms and/or the molecule removes one or more hydrogen atoms.
2. The process of oxidation is usually coupled to a reduction process[[3]](#footnote-3) that is driving it. Together these processes are called oxidation-reduction processes or redox processes. Due to the difficulty of effectively pairing a beneficial oxidation reaction with a beneficial reduction reaction, to oxidize a given substance we often use a sacrificial oxidation compound that undergoes a reduction process as it oxidizes the target material and the sacrificial oxidation compound is degraded during the process without generating meaningful compounds in turn. Consequently, when we speak of the oxidation reaction, we usually ignore the reduction reaction process associated with the wanted reaction.
3. **Figure 5** depicts the oxidation process chain of sulfanyl (also known as a “sulfide”) to sulfate via a sulfinyl (in this document, the sulfinyl will be called by its classical name “sulfoxide”), sulfonyl (also known as “sulfone”) and sulfonate and also the opposite reduction reactions. **Figure 5** shows only a small portion of the many possible redox reactions with sulfur derivatives and it ignores the details of reactions that serve the wanted processes on the sulfur derivatives.

 

 **Figure 5**

The chain of oxidation reactions of sulfanil to a sulfate through di-sulfanyl, sulfinyl, sulfonyl and sulfonat, and the reverse reduction process. The [Ox] mark over the arrow represents an oxidation process while the markup [Red] under the arrow represents a reduction process. The acronym O.S. (O.S. = oxidation state) describes the oxidation state of the sulfur atom. Groups A and A' describe different groups in which the binding is made to the carbon atom.

1. Below, I will focus on the selective oxidation process of sulfides to sulfoxides (the first reaction to the left in **figure 5**), the relevant oxidation reaction for the invention as it was known at the priority date.

 **d.3. Oxidation of sulfides into sulfoxides**

1. At the priority date[[4]](#footnote-4), a wide range and variety of oxidants and oxidation processes were known that enable selective oxidation (some less, some more) of sulphides to solfoxides, whether by **direct oxidation**, in which the oxidizing molecule causes direct oxidation of the oxidized molecule, or through **indirect** **oxidation** in which the oxidizing molecule oxidizes an interim oxidized molecule, which in turn oxidizes the oxidized molecule that produces the desired output.
2. In the literature, a large and varied number of examples of **direct** **oxidation** methods were published. For example, Kaczorowska et al.’s review article from 2005[[5]](#footnote-5) details among other things oxidation reactions of sulfides to sulfoxides in a direct oxidation process in which the oxidizing material is hydrogen peroxide (H2O2)[[6]](#footnote-6).
3. In the direct oxidation of sulfides using a peroxide, such as hydrogen peroxide, the first product will be a sulfoxide (step A **Figure 6**) which will likely continue to be oxidized to a sulphone (step B, **Figure 6**) with a similar mechanism but much slower, which involves a nucleophilic assault of the peroxide group by the sulfur atom in the sulfoxide, and via a mechanism that is generally considered to be more effective and faster in which the peroxide anion attacks as a nucleophil the sulfur atom of the sulfoxide (step B **Figure 6**). Oxidation of the sulfoxide to a sulphone is a common by-product of sulphides to sulfoxides oxidation processes and it affects the selectivity of the reaction and reduces the yield of the desired process[[7]](#footnote-7).

 

 Figure 6

the accepted mechanisms of oxidizing sulfides to sulfoxides (A) and the oxidation of sulfoxides to sulfones (B) by use of a peroxide.

1. Oxidation of a sulfoxide to a sulphone is a common by-product of the sulphides to sulfoxides oxidation processes. It affects the selectivity of the reaction and reduces the yield of the desired process[[8]](#footnote-8).
2. To ensure the selective oxidation of a sulfide to a sulfoxide, the continuation of the process, oxidation of a sulfoxide to a sulfone, must be minimized. Prior art teaches that this can be accomplished by controlling the parameters of the reaction[[9]](#footnote-9).
3. For example, in an article by Hussain et al. (2009)[[10]](#footnote-10) they describe a simple and general method to control the continuous reaction of oxidation of sulfoxides to sulfones in sulfide to sulfoxide oxidation reactions using hydrogen peroxide. The researchers found that **using a peroxide and more specifically, hydrogen peroxide, in acidic conditions inhibits the unwanted sulfoxides to sulfones** **oxidation process**. This probably occurs because the acidic conditions lower the concentrations of the peroxide anion in the reaction solution. The research has also shown that by using a peroxide of the hydrogen peroxide type in similar conditions but in a basic environment will actually encourage the continuous oxidation reaction of oxidizing sulfoxides to sulfones by most probably increasing the concentrations of the peroxide anion in the reaction solution. In basic conditions, the main products are sulfones and in acidic conditions the main products are sulfoxides.
4. Researchers have also shown that when working under gentle conditions (room temperature) and in acidic conditions, selective oxidation of sulfides to sulfoxides can occur with high yields also using molecules that have additional groups that are sensitive to oxidation such as alkenes (C=C), nitriles (-C≡N) and alcohols (-OH).

In addition, Swern in his review paper from 1949 explains that hydrogen peroxide can directly oxidize sulfides. However, the oxidation reaction of sulfides to sulfoxides is more effective when it is done in the presence of an organic acid[[11]](#footnote-11).

1. Someone in the field of developing selective oxidation processes of sulfides to sulfoxides should know or find in the literature, for instance from one of the basic textbooks of organic chemistry[[12]](#footnote-12) and from the sources quoted within, the mechanism of the oxidizing reaction from sulfides to sulfoxides. From the known knowledge at the time of the priority date, someone skilled in the arts should be able to reach the conclusion that to achieve selective oxidation that person should use a peroxide, preferably hydrogen peroxide, which is a commonly found oxidizer, is cheap, safe, “green” to the environment and effective in these types of reactions. A person skilled in the arts should also know that it is preferable to work in an acidic environment in order to inhibit the continuous oxidation process of a sulfoxide to a sulfone. The choice of which acidic environment to use is something routinely done in a lab in which a person skilled in the arts should be able to do with simple instrumentation, based on expected costs of raw materials and processes involved, safety, environmental impact and prior literary knowledge, as detailed below.
2. Many examples have also been published prior to the priority date whereby the oxidizing molecule oxidizes a molecule using an **indirect oxidation** method. Here, the oxidizing molecule uses an intermediate substance (for example dichloroacetic acid or **DCA**)[[13]](#footnote-13) which will in turn oxidize the target molecule, thus yielding the requested product. In some of these reactions the intermediary molecule serves as a catalyst. In some of the cases, the intermediary molecule is produced *in situ* in the reaction vessel. This method has many advantages especially in cases where the intermediary molecule is unstable or not available commercially (either very expensive or not available) and/or unsafe to handle.

In other cases, the intermediary molecule enhances the selectivity of the oxidation in that it preferentially oxidizes the reactant to produce the desired product. In these cases, the main use of the intermediary molecule is to decrease the oxidizing ability of the primary oxidizer in cases where the primary oxidizer is cheap and strong but not specific enough. In these cases, the primary oxidizing molecule oxidizes the intermediary molecule and is degraded. The intermediary molecules are gentler oxidizers and the oxidation reaction done on the reactant is gentler and more selective[[14]](#footnote-14).

1. In the prior art, there are descriptions of oxidation reactions of organic sulfides to sulfoxides in the presence of organic acids such as trifluoroacetic acid (**TFA**)[[15]](#footnote-15), trichloroacetic acid (**TCA**)[[16]](#footnote-16), dicloroacetic acid (**DCA**)[[17]](#footnote-17), chloroacetic acid (**CAA**)[[18]](#footnote-18), acetic acid (**AA**)[[19]](#footnote-19) and other acids[[20]](#footnote-20).
2. In Swern’s review article there is a long list of oxidations of sulfides to sulfoxides in the presence of different types organic peracids and also in the presence of organic acids and hydrogen peroxide thus creating the organic peracid in the reaction vessel (in situ)[[21]](#footnote-21).
3. An organic **peracid** is the product of the oxidation of an organic acid with an oxidizer such as hydrogen peroxide, as described in the example in **Figure 7**. The figure shows an example of the reaction of manufacturing a peracid from an organic acid. In the example, the acid DCA reacts with hydrogen peroxide, creating the peracid, dichloro**per**acetic acid (**DCPA**)[[22]](#footnote-22).

 

 **Figure** **7**

A reaction of the carboxylic acid DCA with hydrogen peroxide to obtain the peracid DCPA.

1. Methods of preparing organic peracids were known already in the beginning of the previous century, much before the priority date, and they are summarized in Swern’s review article from 1949. Greenspan’s[[23]](#footnote-23) article from 1946 also shows a method of preparing a peracid from a reaction between hydrogen peroxide and organic aliphatic acids[[24]](#footnote-24). In a similar fashion, US patent number 2,813,896[[25]](#footnote-25) from 1957 demonstrates a method of preparing a peracid from chloroacetic acid (**CAA**) and hydrogen peroxide. US patent number 3,928,372[[26]](#footnote-26) establishes a method of preparing a peracid from dichloroacetic acid (**DCA**) and hydrogen peroxide.
2. As previously mentioned, the oxidation processes described above, and many others that were not described, were part of the general knowledge in the field on the effective date. On the priority date, a professional in the field had in his hands a variety of substances that could be used to selectively oxidize sulfides to sulfoxides. That person also had a plethora of suitable oxidizers and a series of corresponding organic and non-organic acids from which to choose using simple means the oxidizer and the appropriate conditions.
3. I disagree with the requestor's claim in paragraph 52 of the claims that Swern, Greenspan and 896 are not relevant to the discussion of the present invention as to the degree of novelty[[27]](#footnote-27). The fact that these publications are very old, Swern, for example, references sources that are relevant as background material that are more than a hundred years old, only underscores the breadth of knowledge, basic and detailed on subject of the application, and it is an indication that it is general knowledge that was available and was inherently known to those skilled in the art at the priority date. The extensive and detailed knowledge on the subject of oxidation was used by professionals in the field when weighing their options, and therefore these sources are most relevant in the discussion.

Swern shows that selective oxidation of sulfides to sulfoxides in the presence of hydrogen peroxide and acetic acid (and acetic acid derivatives) was already known in the middle of the previous century[[28]](#footnote-28). He also brings references that are over a hundred years old[[29]](#footnote-29). Being that these methods were not contradicted by newer publications makes Swern’s article very relevant. Similarly, 896 describes a simple and safe method of manufacturing organic peracids with both high yields and concentrations using a reaction of a chosen acid with hydrogen peroxide in concentrations that create safe conditions for the reaction including the peracid dichloroacetic acid (DCPA), that the requestors mention in their patent. Already in 1952, as mentioned in 896, that the purpose of the patent (in 896) is to provide a method of manufacturing peracids using oxidation reactions.

“This invention comprises a process whereby organic peracids may be obtained in good yield and in high concentrations in a technically simple and safe manner. The uses of such organic peracids as oxidation agents, disinfecting agents, bleaching agents and catalysts are well known and have been previously set forth in such publications…”

Greenspan strengthens what is written in 896 and reports not only on a method for producing peracids using hydrogen peroxide at a 30% concentration, which is relatively safe, but also on the stability of the peracid in a solution. This prior art that is brought in these three publications, is only a small fraction of the rich knowledge known to someone skilled in the arts when trying to develop this type of process. These three publications put the current patent application in the correct framework.

**e. The invention that is being claimed in the patent application**

1. The application describes a method (process) for making sulfoxides described by the general formula of the family of substances **I** that are in Figure 4 in which R1 and R2 are independently hydrogen atoms or halogen atoms. The sulfoxides from the family of substances **I** obtained by oxidizing sulfide group of the starting material with the structure described by the general formula of the family substances **II** in Figure 3, where R1 and R2 are independently hydrogen atoms or halogen atoms.
2. In the application there is one main claim (claim number 1) and 15 dependant claims.

 **e.1. Claim number 1**

1. The oxidation reaction according to the invention, as it is defined in claim number 1 in the patent application, is schematically described in **Figure 8**.

 

 **Figure 8**

A schematic representation of the oxidation reaction according to the invention, as is defined in claim number 1 in the patent application.

1. Claim number 1 is the only independent claim in the patent application and all fifteen other claims are dependent on this claim either directly or indirectly. In the following Table, I will analyze the different parts of claim number 1:

|  |  |
| --- | --- |
| IL 221005 application | Element |
| Method for the preparation of | a |
| The compound having the following general formula (I):wherein Rl and R2 are independently hydrogen or halogen | b |
| through oxidation of a compound having the general formula (II):wherein Rl and R2 are defined as above | c |
| in the presence of dichloroacetic acid [DCA][[30]](#footnote-30)  | d |
| and of an oxidizing agent | e |
| where the oxidizing agent is selected from the group consisting of: benzoyl peroxides, sodium peroxidest-butyl peroxides and/or hydrogen peroxide,  | e1 |
| and wherein the oxidation is conducted in the absence of trichloroacetic and/or trichloroperacetic acid. | f |

1. The method in claim 1 of the patent application is the oxidation of a compound from the family compounds **II** to a compound of the family of compound **I** (elements a-c). The oxidation is done in the presence of dichloroacetic acid (**DCA**, element d) and an oxidizing agent selected from a group oxidizing compounds (elements e and e1) and in the absence of trichloroacetic acid (**TCA**) and or trichloroperacetic acid (**TCPA**, element f).
2. In the manner that claim 1 is formulated, I understand that they are claiming **every oxidation method** of the family of compounds **II** to achieve the corresponding product from the family of compounds **I** with these exceptions:

40.1 the chosen oxidizers are from the following list that includes hydrogen peroxide and three other **families** of oxidizers (benzoyl peroxides, sodium peroxides, t-butyl peroxides) which include many oxidizers many of them are common and known.

40.2 The oxidation occurs in the presence of **DCA**

40.3 The oxidation occurs in the absence of **TCA** and/or **TCPA**.

1. Therefore, the definition in claim 1 covers reaction conditions in which other substances also exist, such as solvents, acids, peroxi-acids, bases, peroxi-bases, catalysts, additives to prevent corrosion and any other material. In addition, claim 1 covers all the reaction conditions in terms of temperature and temperature regimens, acidity and acidity regimens, methods of adding ingredients and ingredient adding regimens plus many other variables such as the molar relationship of the materials found in the reaction container, their absolute quantities, types of processing before and after the reaction, use of various types of reaction vessels and other variables not specifically mentioned in it but also not excluded from the claim.

**e.2. The dependent claims**

1. **Claim number 2** is dependent on claim 1 and limits it to materials in which R1 and R2 are chlorine and bromine.
2. Claim number 3 is dependent on claims 1 and 2 and it limits them in that the material from the family of compounds I is 5-amino-1-(2,6-dichloro-4-trifluoromethyl-phenyl)-4-trifluorometansulfinyl-1H-pyrazole-3-carbonitril, (**1**).
3. **Claim number 4** is a claim that is dependent on all the previous claims and it limits them in that **DCA** is oxidized to **DCPA** by any oxidizing reagent listed in claim 1.
4. **Claim number 5** is dependent on claim number 4 and it limits it in that the oxidizing process of **DCA** to **DCPA** occurs in the reaction vessel (originally defined as *in situ*[[31]](#footnote-31)).
5. **Claim number 6** is dependent on all previous claims and it limits them in that for every mole of material from the family of compounds **I**, 1.0-5.0 moles of an oxidizing agent will be used.
6. **Claim number 7** is dependent on all the previous claims and it limits them in that for every mole of material from the family of compounds **I**, 1.0-2.0 moles of an oxidizing agent will be used.
7. **Claim number 8** is dependent on all the previous claims and it limits them in that for every mole of material from the family of compounds **II**, 1.5-5.0 kilograms of DCA will be used.
8. **Claim number 9** is dependent on the previous claims and limits them in where the reaction takes place between 0 and 35 Co[[32]](#footnote-32).
9. **Claim number 10** is dependent on the previous claims and limits them in where the reaction takes place between 0 and 20 Co where the preferred temperature is 5 Co.
10. **Claim number 11** is dependent on the previous claims and limits them in that it adds an additional step in which the material from the family of compounds **II** that did not undergo oxidation is collected.
11. **Claim number 12** is dependent on claim 11 and limits it in that the material from the family of compounds **II** that did not undergo oxidation is collected and then undergoes consecutive processes of dissolution and recrystallization of the material from the family of compound **I** with one or more solvents selected from the following group: toluene, xylene, chlorobenzene, chlorinated aliphatic solvents, and isopropanol.
12. **Claim number 13** is dependent on the previous claims and limits them in that the oxidation process of the family of compounds **II** occurs in the presence of an acidic catalyst.
13. **Claim number 14** is dependent on claim number 13 and limits it in that the acidic catalyst is a strong mineral acid from a group containing sulfuric acid, methanesulphonic acid, hydrochloric acid, nitric acid and their mixtures.
14. **Claim number 15** is dependent on claims 13 and 14 and limits them in that the molar ratio between the material from the family of compound **II** and the acidic catalyst is between 0.3 and 1.5 where the preferred molar ratio is 0.7.
15. **An additional claim number 15** - In the application form as it appears in the Registar's website, claim number 15 appears twice. The additional claim 15 is dependent on claim number 1 and limits it in that the oxidizer is hydrogen peroxide.
16. As mentioned above, the claimed oxidation process conditions can be learned from the language of the claim as set out in paragraph 40 above, but can also be learned from the scope of its dependent claims. From the reduction of the main claim by the dependent claims, I can learn, among other things, that claim 1 includes by implication the following:
	1. From the limitation of claim 1 by dependent claim 4[[33]](#footnote-33) it seems that claim 1 covers methods in which **DCA** is not oxidized to **DCPA**. The meaning of claim 4’s limitation is that claim 1 also covers direct oxidation of materials from the family of compounds **II** by oxidizing compounds (or compound) that are in the list appearing in claim 1 and/or indirect oxidation processes mediated by other materials not expressly claimed.
	2. From this we see that oxidation of a compound **II** can be done by **DCPA** or by any other peracid which is not **TCPA**, for example **TFPA**[[34]](#footnote-34). Moreover, the oxidation of materials from the family of compound **II** can also be done directly by the oxidizer found in the system, for example benzoyl peroxide or hydrogen peroxide, that instead of reacting with **TFA** or **TCA** can directly oxidize the compound **II**.
	3. Reducing claim 1 through dependent claim 5[[35]](#footnote-35) indicates that oxidation according to the invention as defined in claim 1[[36]](#footnote-36) can also be made by **DCPA** that is not formed *in situ*, but is generated outside the system and is added as an oxidizer in the reaction of compound **II**.

**f. The invention that is being claimed is not novel**

1. As stated above, the invention as defined in the claims, describes a method for the oxidation of the starting material, a compound from the family compound **II** to a product, the corresponding compound from the family of compounds **I**. Most of the method that is claimed in the invention is included in full in the description and claims of the Australian patent application AU 2010100462 A4 (**462**), titled: A Process for the Synthesis of Fipronil. The **462** application was published before the priority date, on 17 June 2010.
2. In the body of the application and in claim 1 of application **462** there is a description of a multi-step process for making Fipronil and similar products included in a general formula that overlaps with the family of compounds **I** according to the application[[37]](#footnote-37). Step **i** of the process in application **462** is the oxidation of the starting material that has a general formula **IX** that overlaps with the family of compounds **I** in the application[[38]](#footnote-38). Here is the language for step **i** in claim 1:

*"Oxidizing the isolated thio pyrazole compound of formula IX in a reaction medium comprising a oxidizing agent, preferably the oxidizing agent is a peroxide compound* *selected from the group consisting of hydrogen peroxide, tert-butyl hydrogen peroxide, benzoyl peroxide and sodium peroxide, preferably hydrogen peroxide in the range of 0.8 to 1.2 molar equivalent ; a solvent system; and a corrosion inhibitor, preferably boric acid, to yield a product mixture containing trifluoromethyl sulfenyl pyrazole compound of formula I."*

1. In the table below, I will examine the different elements of claim 1 in the patent application as presented above[[39]](#footnote-39) and compare them to claim 1 and to the provided details in the body of patent application **462**.

|  |  |  |
| --- | --- | --- |
| According to AU 2010100462 A4 | According to Claim 1 of IL 221005 | Element |
| Claim 1: A process for the preparation of a trifluoromethylsulfenyl pyrazolecompound of formula 1, wherein Rl, R2 contain elementsof halogen group respectively,; and R3: isperhaloalkylClaim 1(i)"to yield a product mixture containing trifluoromethyl sulfenyl pyrazole compound of formula I" | Method for the preparation ofthe compound having the following general formula (I):wherein Rl and R2 are independently hydrogen or halogen; | a + b |
| Claim 1(i)oxidizing the isolated thio pyrazole compound of formula IX  | through oxidation of a compound having the general formula (**II**) | c |
| Claim 1- a solvent systemPage 12 lines 21-25In preferred embodiment of the present invention, the solvent system in oxidation step (i) is a mixture of at least two solvents selected from a group of halogenated solvents consisting of trifluoroacetic acid, trichloroacetic acid,dichloroacetic acid, chlorobenzene, dichloromethane and dichloroethane | in the presence of dichloroacetic acid  | d |
| Claim 1(i)preferably the oxidizing agent is a peroxide compound selected from the group consisting of hydrogen peroxide, tert-butyl hydrogen peroxide, benzoyl peroxide ,and sodiumperoxide, preferably hydrogen peroxidePage 13 line 24-26 The oxidizing agent is a peroxide compound selected from the groupconsisting of hydrogen peroxide, tert-butyl hydrogen peroxide, benzoylperoxide and sodium peroxide. | and of an oxidizing agent:and where the oxidizing agent is selected from the group consisting of benzoyl peroxides, sodium peroxidest-butyl peroxides **and/or** hydrogen peroxide,  | e+e1 |
|  | and wherein the oxidation is conducted in the absence of trichloroacetic [**DCA**] and/or trichloroperacetic acid [**DCPA**]. | f |

1. **To summarize**: To the best of my understanding, all the parts of the invention that is claimed in the patent application have already been published in **462**. I will give a detailed explanation on the different elements from the above Table.
2. **The family of product material (elements a+b from the Table):** There is an overlap between the family of compounds **I** of the patent application to the family of compounds **I** in **462**[[40]](#footnote-40).
3. **The family of compounds that are oxidized (element c from the Table)**: There is an overlap between the family of compounds that are oxidized, the family of compounds **II** in the patent application and the group of compounds **IX** in **462**. The functional group that is oxidized to a sulfoxide is the same along with the neighboring functional groups[[41]](#footnote-41).
4. **The solvent in the reaction (elements d + f in the Table)**: The invention claimed in the patent application requires the presence of **DCA** in the oxidation process, but does not exclude the presence of other substances in the solution, except for **TCA** and/or **TCPA**. The possibility of the presence of other substances in the process is implied, among other places, in the dependent claims[[42]](#footnote-42). Some of the examples described in the oxidation process in **462** include the use of a solution containing **DCA** (together with other substances). In addition, in the description of application **462** there is a preference to use solvents comprising of a mixture of solvents (at least two solvents) from a specific list that includes **DCA**. However, the description in patent application **462** certainly does not rule out the possibility of using a single solvent, and in particular a single solvent from the recommended list above, such as **DCA**. My conclusion is that there is an overlap between the solvent component in patent application **462**, and the solvent component in the patent application.
5. **The oxidizing material (element e + e1 in the Table)**: Each of the family of claimed materials in the patent application is represented by at least one substance in patent application **462** that precedes the contested patent application. In **462** they are explicitly mentioned as preferred application, as described above. The oxidation process claimed in the patent application for all components was predated by patent request **462**. Therefore, I think there is no novelty in this patent application.
6. I do not agree with the way the petitioner describes[[43]](#footnote-43) what was revealed in publication **462**, as well as the petitioner's arguments based on this publication.

Indeed, **462**, teaches and claims a more comprehensive synthesis process than the patent application. However, this has no bearing on the fact that in the body of application 462 there is a description of isolating the product in phase **IX**[[44]](#footnote-44). For instance in example 12 there appears the yield of a material from family **IX**, a detail that requires the isolation of the material[[45]](#footnote-45). Example 13 describes the process of oxidizing material from the family of **IX**, describes the weighing of the material and adding it to the reaction vessel[[46]](#footnote-46). Also in claim No. 1 section (**i**) of **462**, it explicitly appears that the oxidation process is performed on material from the family of materials **IX** that underwent isolation[[47]](#footnote-47). Therefore, in my understanding, the fact that the description and claims of application **462** mentions a more complex process has no meaning (if anything, these facts can be construed as an indication that the inventor of request **462**, did not see this process in itself as a novel invention), and we can focus the discussion on the oxidation process described in it as an independent process.

1. The petitioner shows a variety of examples listed in application **462**, and claims that it "teaches that the oxidation step is carried out in a mixture of trifluoroacetic acid and/or trichloroacetic acid and at least one other solvent selected from the list that includes chlorobenzene, dichloroacetic acid, dichloromethane and dichloroethane. Indeed, application **462** teaches that, **but not only that**. Application **462** shows clearly that:

*“In preferred embodiment of the present invention, the solvent system in oxidation step (i) is a mixture of at least two solvents selected from a group of halogenated solvents consisting of trifluoroacetic acid, trichloroacetic acid, dichloroacetic acid, chlorobenzene, dichloromethane and dichloroethane.”*[[48]](#footnote-48)

1. From these lines, it is clear that the inventor's recommendation is to use a solution consisting of a mixture of solvents, at least two, from a defined group of solvents, including dichloroacetic acid. However, this is only in the preferred embodiment, and the description indicates that you can use a solvent that is not a mixture, including the use as a solvent only of dichloroacetic acid, **DCA**, or a mixture of solvents which include dichloroacetic acid.
2. Since application **462** mentions hydrogen peroxide (and others) as the oxidizing material in the reaction[[49]](#footnote-49), it reveals the possibility to use dichloroacetic acid (**DCA**) as a solvent and hydrogen peroxide as an oxidizer.
3. The legal counsel of the opposing party explained to me, and I accept the explanation, that an invention is not considered novel if before the priority date, a publication was published in a way that someone skilled in the arts could duplicate it according to what was written in the aforementioned publication. It was also explained to me that the reading of someone skilled in the arts of a previous publication takes into account that the said person has general knowledge in the field of the invention.
4. **Therefore, due to the facts that all the components of the petitioner’s method were described in application 462 in a way that someone skilled in the arts could duplicate the experiment at the priority date, demonstrates that there is no novelty in the patent application.**
5. Moreover, I will note that I totally disagree with the petitioner's argument that "a person skilled in the arts would easily understand that dichloroacetic acid is used to lower the melting point and therefore cannot be used for the oxidation of the sulfide intermediate."
6. This argument is not reasonable also due to the reason that as a solvent, dichloroacetic acid has no obvious advantages over a long list of common and much cheaper solvents, with much lower melting points. The only implicit advantage of this acid is that it can be basically used as a secondary oxidizer in the oxidation process.
7. The argument that application 462 "confirms the determination of Gharda in application 440, the dichloroacetic acid is a "poor medium for oxidation and the only purpose of its addition is to depress the melting point of the trichloroacetic acid" has no basis in light of the above. A person skilled in the arts would conclude from application **462** and from previous knowledge in the field that do not apply to Gharda's conditions in application **440** regarding dichloroacetic acid, and that it can be used as a medium in oxidation processes.

**g. The use of DCPA to someone knowledgeable in the field is obvious and there is no novelty in DCPA oxidation**

1. One of the arguments that are brought in the beginning of patent application IL 221005 is a supposedly unanticipated result and due to that, the claim for a patent in that one can use **DCPA** as an oxidizer (page 6 lines 12-19 in the patent application).

*“the use of dichloroperacetic acid as an oxidant has never been described in the literature. Surprisingly it was found that DCA, in the presence of an oxidant species such as hydrogen peroxide, peroxide or similar, is also itself transformed at low temperatures into the corresponding dichloroperacetic acid and that this species is an excellent oxidant of the compound having the general formula(****II****).”*

In this paragraph there are two establishments of facts: the first claim is that the use of **DCPA** as an oxidizer was never before described in the literature. The second is that **DCA** in the presence of a peroxide or similar oxidizer, at low temperatures, becomes **DCPA** and that this material (**DCPA**) can be used as an excellent oxidizer for materials from the family of materials **II**. I do not agree with the first claim and I do not agree with the claim that there is any unanticipated surprise in the second claim’s process.

1. Firstly, as was detailed in chapter d.3., the use of DCPA in oxidation processes that include an oxidizer and **DCA** was described in available publications before the priority date[[50]](#footnote-50).
2. Secondly, in the light of general knowledge in the field before the priority date, there should not have been any unanticipated result that **DCA** acid would become its peracid, **DCPA**, in the presence of an oxidizer such as hydrogen peroxide, something that was many times described in the literature prior to the priority date[[51]](#footnote-51). Also previously described is that this material is a suitable oxidizer for compounds from the family of compounds **II** to obtain products from the family compounds **I** with high yields.
3. Before I deal with specific publications, I will detail a number of basic principles in the work of those skilled in the field that are tasked with developing a process of oxidation of materials from the family of compounds **II** to products from the family of compounds **I**.
4. In designing an oxidation reaction, the chemist has a choice of a vast variety of oxidizing agents, organic and non-organic, which from them the chemist has to choose the appropriate reactants and the optimal reaction conditions.
5. A common way to reach the oxidation reaction conditions that suit the desired response includes, among other things, characterization of the starting reaction material and defining the possible adverse reactions. For example, in the family of the starting materials from the family of compounds **II**, the sulfur atom is not the only possible reacting atom and is not the only possible oxidation reaction site. Therefore, there is a requirement that the oxidation will be done with a high enough preference on the appropriate functional group (in our case, a sulfur atom) and to the degree of wanted oxidation (in our case, a sulfur atom should switch from an oxidation level of (-2) in the sulfide to an oxidation state of (0) in a sulfoxide). This process should be carried out without significantly harming any other groups in the existing starting material from the family of compounds **II** and from the product from the family of compounds **I**, and without the continued oxidation of the product, a sulfoxide from the family of compounds **I**, to a sulfone.
6. One of the important and central steps that are routinely done in such cases in selecting an oxidizer and reaction conditions is conducting a literature survey. The goal is to determine the identity of the oxidizer (or oxidizers) and reaction conditions that are known to carry out the desired oxidation reaction for one or more from the family of compounds **II**, and/or of chemical structures that are "relatives" of the family of compounds **II** (for example a similar derivative from the family of compounds **II**).
7. For the oxidation of compounds from the family of substances **II** to a compound from the family of substances **I**, there are few examples in the literature. Most of them are regarding a commercially interesting material, Fipronil. In appendix [20] we have the results of specific searches using the Scifinder software and defining the desirable reactants and product, which will change according to the degree of freedom allowed in the software in recognizing the reactants and products (we were not able to limit the search to prior to the priority date). It can be seen that the number of reactions known grow as we continue to expand the family of materials that we were looking for. From the references listed in the search results it can be seen that the major byproduct of most of these reactions is a sulphone.
8. Another literature review that an average profession in the field would perform will focus on the overall reaction that is to be done, the materials and conditions suitable for the reaction to occur, the desired level of purity, its mechanism, and its common byproducts. In the present case, a professional working in a routine fashion will learn about the oxidation of sulphides to sulfoxides and the ways to achieve a selective process as much as possible and avoid getting sulphonated byproducts. In published material about the desired reaction and similar reactions, the professional will search for the preferred oxidizing substance and for the reaction that he is planning to carry out. In addition he will seek the solvent or solvents and reaction conditions used in the past. What I mean by the term "the preferred" is that there are different considerations in selecting materials, such as the availability and price, and on that I will further expand bellow.
9. A review of our search results in Appendix [20] (after deducting the published comments after the priority date) shows that it was already known how to carry out the desired oxidation reaction and others like it in a variety of ways with good to excellent yields[[52]](#footnote-52).
10. Most of the oxidation reactions include the use of hydrogen peroxide or other organic peroxides as an oxidizer. These reactions also include the use of a solvent or a mixture of solvents. The prior art teaches that the oxidation reaction of a compound from the family compounds **II** to a compound from the family compounds **I** and similar systems can be performed with high efficiency using a combination of hydrogen peroxide as an oxidizer and **TCA**[[53]](#footnote-53) and/or **TFA**[[54]](#footnote-54) as mediators in the oxidation reaction.

Similarly, it is anticipated that additional acids from the same homologous series will show similar redox properties, with their properties changing gradually from derivative to derivative[[55]](#footnote-55). Three of the acids that are closest to **TCA** and **TFA**, which were the first candidates for the experiment were difluoroacetic acid, dichloroacetic acid (**DCA**) and tribromoacetic acid. A person skilled in the arts had no reason to assume that the **DCA** would not be an effective oxidizer similar to **TCA**. On the contrary, according to the known general knowledge in the field before the priority date it was known that this acid can be used in the process of indirect oxidation of sulphides to sulfoxides and for oxidizing materials from the family of compounds **II** to substances from the family of compound **I**, such as Fipronil[[56]](#footnote-56), which strengthens my view that the average professional would choose **DCA** as one of the first choices. There also were no technological barriers preventing the person skilled in the arts from using **DCA** instead of the **TCA**, and as previously mentioned, the use of **DCA** was suggested by the Australian publication expressly denying to my understanding any novelty in this invention. In addition, the Swern publication indicates that a significant disadvantage of trichloro peracid acetic, **TCPA**, is that it is extremely unstable and that it speedily degrades into active ingredients, such as phosgene, chlorine and hydrochloric acid, whereas monochloro acetic acid, **MCPA**, is stable enough to undergo purification by distillation[[57]](#footnote-57). If only for this reason, there is good reason to think that a professional in the field would examine the possibility of using **DCA** as a means to combine stability, reactivity and safety.

The first publication showing that trichloro acetic acid, **TCA**, can be used as an effective mediator in the process of oxidation (not as the only solvent because it is solid at room temperature), would direct the attention of a professional in the field to use a line of homologous chlorine derivatives of acetic acid, such as **DCA**, as oxidation mediators in the oxidation process, and even more so when there were specific publications about oxidation processes of starting materials from the family of materials **II** to substances from the family of materials **I** in which trichloro acetic acid has been reported to be effective in mediating oxidation processes.

In the line of homology of the chlorine derivatives of acetic acid are three relevant derivatives when only one of which is characterized by a low melting point and can be used as the solvent and it is **DCA**. In addition, from all the derivatives, **DCA** is expected to be the closest to **TCA's** chemical properties. Therefore, this chemical would be is the first compound that a routinely acting professional would choose to try.

1. The table below describes a series homologous halogen derivative of acetic acid and the acidity dependent nature of the number and type of halogen atoms that it has. It is not surprising to see that an increase in the number of halogen atoms increases the acidity of the acid. In addition, with an increase of the atomic number of the halogen atom, there is a decrease in the acidity of the acid. [This material I teach in a basic course in organic chemistry for non-chemists (e.g. medical students) at the Technion, Course No. 125 801. Attached as **Appendix 21** are the relevant course presentation slides[[58]](#footnote-58).
2. It should be noted that the strength of an acid is shown in its pKa value. The stronger the acid the lower the pKa value is. In addition, the melting point of these derivatives were also known.

|  |
| --- |
| **Table 2: homologous series of halogen derivative of acetic acid and the pH dependency in the nature and number of halogen atoms that the derivatives have** |
| **CH3COOH**pKa=4.76 (25C)a |  |  |
| **CH2FCOOH**pKa=2.59 (25C) a250mg=595 ILS (Sigma-Aldrich)Mp=+35 °C | **CHF2COOH**pKa=1.24b25g=1,658 ILS (Sigma-Aldrich) Mp=−1 °C  | **CF3COOH**pKa=0.52 (25C)aCRC3kg=3,898 ILS (Sigma-Aldrich)Mp=−15.4 °C |
| **CH2ClCOOH**pKa=2.87 (25C) a1kg=268 ILS (Sigma-Aldrich)Mp=+63 °C | **CHCl2COOH**pKa=1.35 (25C) a3.9kg=1040 ILS (Sigma-Aldrich)Mp=+9-11 °C | **CCl3COOH**pKa=0.66 (20C) aMp=+57-58 °C  |
| **CH2BrCOOH**pKa=2.90 (25C)a2kg=1,498 ILS (Sigma-Aldrich)Mp=+47-49 °C | **CHBr2COOH**pKa=1.47c25g=1,150 ILS (Sigma-Aldrich)Mp=+32-38 °C | **CBr3COOH**pKa=0.72d25g=411 ILS (Sigma-Aldrich)Mp=+128-132 °C |
| **CH2ICOOH**pKa=3.18 (25C)a 100g=1,152 ILS (Sigma-Aldrich)Mp=+77-79 °C |  |  |
| a: CRCb: Acetic acid and its derivatives c: Chemical dictionary d: Guidechem  |

1. In the industry, where there are different constraints than those in research laboratories, a reasonable effort will be made to use oxidizing agents that are readily available and cheap and/or those that can be recycled in an inexpensive way. Some additional considerations in the manufacturing process of selecting the oxidizing agent would be safety considerations (some of the oxidative materials are explosive and dangerous to store and work in bulk), human toxicity (some of the oxidative materials are known to be carcinogenic and/or toxic) and toxic to the environment (some of the oxidative materials are known to be toxic and as such, damaging to the flora and fauna around us).
2. For example, tribromo acetic acid which is homologous to **TCA** and TFA is expected to fit in terms of the pKa value but will not necessarily be used in the industry because of its high melting point, the high costs of bromine compounds, and the possibility of other adverse reactions due to the fact that the carbon-bromine bond is significantly weaker than the carbon-carbon or even the carbon-chlorine bond.
3. In a similar way, it is not likely that the industry will use difluoroacetic acid for oxidation because of its scarcity and its much higher price as compared to **TCA**.
4. Conversely, **DCA** is a widely available and cheap material with a low melting point (a liquid at room temperature). **DCA** has a pKa that fits and it seems like a candidate that will be able to carry out a selective reaction.
5. In light of the general knowledge in the field, I conclude that a skilled person who wanted, at the priority date, to oxidize a material from the family of compounds **II** to get a product from the family of compounds **I**, would probably use the process claimed in the patent application on all the listed components listed, with a high expectation of success. In particular, the use of **DCA**, the use of representatives from each of the oxidizer families mentioned in the request, with the same or similar reaction conditions specified in the application (such as temperature and time, concentrations, molar ratios etc.) as stated and expected from the average professional mentioned in the request itself[[59]](#footnote-59).

**h. The invention claimed in claim 1 is obvious based on a series of previous publications**

1. In this chapter, I will present publications in relation to the invention claimed in the application before the priority date. As I understand it, these publications, both in themselves and with the general knowledge that existed in the area prior to the priority date, strip all novelty from the claimed patent and make the patent obvious. From the opposing side's representatives, I learned that one publication of those described below, or a combination of such publications with the general knowledge in the field known at the priority date is enough for the invention to be considered obvious and there is no need for the totality of the publications to show obviousness.
2. In addition, and as I explained above, I believe publication **462** revealed all the components of the invention and therefore, if it is clear that if the invention is not new, there cannot be in any case, any unexpected result. In this section, I will not refer back to publication **462**, but it is clear that this publication, combined with the previous knowledge, makes the invention obvious.

 **h.1. The invention claimed in claim 1 was obvious in light of publication #760 and**

 **the basic general scientific knowledge that was known in the field**

1. Publication **760** of Aventis Cropscience SA from 2001, entitled “Process for Preparing 4- Trifluoromethylsulfinylpyrazole Derivates”, describes, among other things, the oxidation of the sulfide starting material (some of them from the family of compounds **II**) to a sulfoxide (some from the family of compounds **I**). Oxidation is done through an organic peracid of the type trifluoroperacetic acid (**TFPA**) obtained as a result of the oxidation of **TFA** by a peroxide, either in situ or in a separate system[[60]](#footnote-60), and in the presence of a substance that prevents corrosion (resulting from the formation of the hydrofluoric acid byproduct, **HF**). To my understanding, the invention in publication **760** on this issue is not the use of **TFA** with hydrogen peroxide to oxidize a sulfide to a sulfoxide, a process known years before this publication[[61]](#footnote-61), but to improve the reaction by using a material that prevents corrosion and prevents the damage caused by hydrofluoric acid.
2. A person skilled in the arts who is aware of the purpose of using **TFA** for oxidation as described in Publication **760** would assume that one can substitute **TFA** and its oxidation product **TFPA** with other acids from the same homologous series or other close substitutes, as explained above[[62]](#footnote-62), are many. As of the priority date it has been already published that the process can be performed efficiently and with high purity of up to 95% in the presence of **TCA** and hydrogen peroxide (probably creating **TCPA**[[63]](#footnote-63)) so that by doing what would be considered routine will result in the halogen derivatives of acetic acid will be the first materials to be examined. **DCA** is a chlorine derivative of acetic acid and generally more affordable and available than the fluorine and bromine derivatives. There was nothing in the collective wisdom of the previous published material that would dissuade and divert a person skilled in the arts to try and use **DCA** and there was no publication that even indicated that such an oxidation is not possible. On the contrary, the general knowledge of a person skilled in the arts would make it crystal clear that the **TFA** analogs would be the first candidates to replace **TFA** in the reaction.
3. I do not agree with the arguments of the petitioners in section 11 of the appeal letter and of the interpretation therein of publication **760**[[64]](#footnote-64). Publication **760** teaches that certain oxidizing agents were found inadequate for one reason or another:

*A number of oxidants (including amongst others sodium vanadate, sodium tungstate, peracetic acid, performic acid and* ***pertrichloroacetic acid****)**[****TCPA****] have been employed in an attempt to obtain an efficient and region selective oxidation which will provide 5-amino-1- (2, 6-di chloro-4-trifl uoromethy l pheny 1)-3 -cyano-4- trifluoromethylsulphinylpyrazole in pure form and which may also be utilized for large scale preparations.* ***All of the above methods were found to be unsatisfactory in one respect or another*** *[[65]](#footnote-65).*

1. The last sentence in the above quotation establishes a very general and vague assertion (in one respect or another) that could have been based on considerations and/or constraints that do not exist in someone skilled in the arts reading publication **760**.
2. The fact that in 2001, a number of specific substances were found inadequate for whatever reason in the experimental conditions that they were tested, does not necessarily mean that such a reaction is not possible and it is doubtful if a skilled person would have attached any significance in light of the general knowledge in the field.
3. In 2010 (before the priority date), a skilled professional in the field, who knew publication **440** from 2007, that taught about the efficient oxidation of materials from the family of compounds **II** to products from the family of compounds **I**, using **TCPA**, would have attached to the general claims that were published in publication **760** from 2001, limited significance if any. In any case, this is a bit of a theoretical discussion in light of the Australian publication **462**, which was also known to those skilled in the art before the priority date.

 **h.2. The invention claimed in claim 1 was obvious in light of publication 440 and**

 **the basic general scientific knowledge that was known in the field**

1. Publication **440** of Gharda et al, entitled “Process for the Preparation of Fipronil”, published in 2007, describes the oxidation of the starting sulfide material with a structure overlapping the family of compounds **II** to a sulfoxide with a structure overlapping the family of compounds **I** (which includes Fipronil). The oxidation is done in the presence of **TCA** and one or more oxidizing materials, or in the presence of the reaction product or products of **TCA** with oxidizing material (or materials) and in the presence of at least one material that lowers the melting point (melting point depressant).
2. According to one of the options in publication **440**, oxidation of the family of compounds **II** is done by a peracid of the type trichloroperacetic organic acid (**TCPA**) obtained as a result of the oxidation of **TCA**, in situ or in a separate system[[66]](#footnote-66).
3. According to Publication **440**, one of the possible materials that can be used to lower the melting point of the mixture is **DCA**[[67]](#footnote-67). In addition, publication **440** also shows that in the conditions described, **DCA** is an inferior oxidizer to **TCA**. However, notwithstanding the above, and even if someone skilled in the arts was of the opinion that **TCA** was more effective than **DCA** to perform the desired reaction, it would not stop any skilled person to try and use **DCA** as the reaction solvent for reasons stated in the discussion section in publication **760**.
4. A skilled person does not read Publication **440** isolated from the general knowledge in the field. The general knowledge clearly taught that the entire line of homologous chloroacetic acids is suitable in principle for selective oxidation of sulphides to sulfoxides[[68]](#footnote-68). Therefore, publication **440** would not stop a person skilled in the arts from trying to use **DCA** as an oxidizer. As explained above, such a step would be routinely carried out by a skilled person who wishes to oxidize material from the family of substance **II** to a product from the family of substances **I**.
5. According to basic scientific knowledge, when **DCA** reacts with an oxidizer, such as hydrogen peroxide, it can be oxidized to an organic peracid, **DCPA**[[69]](#footnote-69). Organic peracids are known as strong oxidizers in reactions of sulphides to sulfoxides[[70]](#footnote-70), and therefore, it is not likely and we cannot rule out the possibility that **DCA** is an active participant in the oxidation process according to the method in publication 440.
6. I disagree with the manner in which the petitioner reads publication **440** in paragraphs 13-15 of the letter of appeal. In publication **440**, the oxidation of a compound from the family of compounds **II** was done in the presence of **TCA** and **DCA**. Even though the stated purpose of the addition of **DCA** according to Publication **440** was to reduce the melting point of **TCA**, this did nothing to deny or exclude the use of **DCA** without TCA for someone skilled in the arts.
7. It was not argued in publication **440** that **DCA** is not oxidized to **DCPA** and is not a suitable reagent for the oxidizing reaction. What was said was that under the conditions of the method (for example, the ratio of the concentrations, temperature, the method of addition and other variables that were unspecified in the publication) the role of **DCA** was to lower the melting point of **TCA**. Substantiating the claim that the average skilled person would understand that for example, **DCPA** created from **DCA** and hydrogen peroxide in situ can be used as an oxidizer can be found even in the applicant's patent application in which it is explained that the reason that **DCPA** oxidation reaction is not described in publication **440**[[71]](#footnote-71) is not because that **DCA** is able to make **DCPA** and oxidize the compound from the family of compounds **II**, but because in this specific system, **DCA's** concentration is low compared to **TCA**:

*“In addition, it is realistic to believe that, in the teaching of the prior art document WO 2007/122440A1, the dichloroacetic acid does not transform into dichloroperacetic acid by means of the hydrogen peroxide or other oxidant, because the species TCA, present in significant molar excess of the oxidant and more reactive towards the oxidants, captures all the available oxygen”*

1. In view of the above, I disagree with the argument of the petitioner[[72]](#footnote-72) as if a skilled person in the field did not think it appropriate to try **DCA** as a solvent and the starting material for **DCPA** as an oxidizer in the reaction. Again, this is somewhat of a theoretical discussion in light of the Australian publication **462**, which was also known to those skilled in the arts before the priority date.

 **h.3. The invention claimed in claim 1 was obvious in light of publication #761 and**

 **the basic general scientific knowledge that was known in the field**

1. Publication 761, entitled “Oxidation of Polyarylene Sulfides” describes a method for the oxidation of sulfides to sulfoxides. According to the method, oxidation is done in the presence of acid and hydrogen peroxide. A detailed list of preferred acids in the publication includes among other **TFA**, **TCA** and **DCA** with the same degree of preference[[73]](#footnote-73):

*"Particularly preferred acids are concentrated sulfuric acid, methanesulfonic acid, trifiuoromethanesulfonic acid, trichloromethanesulfonic acid, chlorosulfonic acid, trifluoroacetic acid, trichloroacetic acid and dichloroacetic acid."*

1. Publication **761** teaches and lists in examples 13-16 the method's components and demonstrates its effectiveness. An average person skilled in the arts who wanted to change from using **TCA**, for instance because of a preference resulting from a high melting point, instability or the tendency to form byproducts that are dangerous and reactive, that person would try with a high degree of expectation of success, to substitute **TCA**, as described in 440, with **DCA** according to publication **761**. For example, if in my lab, a Master's student would have switched the described use from **TCA** to **DCA** for the purposes of a reaction as noted, and the conversion would be successful, it would not be a surprise (it would be a surprise to me if the conversion was not successful). Similarly, it would have been obvious to an average professional in the field who would want to use a material other than **TFA** as published in **760**, to try, with a high level of expectation for success, to substitute this material with **DCA** according to publication **761**.
2. I do not agree with the argument of the petitioner in paragraph 49 of the letter of appeal and of the conclusions which are derived from this argument. Indeed, patent **761** teaches the oxidation of polyarylene sulfide to polyarylene sulfoxide and indeed it discusses the oxidation of polymers. But the conclusion that the scientific field of polymers is different from the scientific field of application 221,005 is entirely incorrect. The chemistry is the same chemistry. This is basic chemistry which is common to all areas. The thought that a skilled person would have believed that oxidation of a sulfide polymer is different from oxidation reactions in the pharmaceutical field or in the field of pesticides seems detached from reality. The reactants, products and reagents in the solution are not aware of the existence of a "polymers field".
3. Polymers will react differently than small molecules (which are, by implication, the claimed "scientific field" of application 221005) when there exists chemical or physical reasons that stem from the properties resulting from size differences between small molecules and polymers, such as partial melting of the polymer, a polymer's aggregation in a solution, precipitation of the polymer after a partial reaction, steric inhibitions to a reaction due to the size of the substituents on the polymer and similar considerations. In all other cases where there are no constraints arising from the unique features of the polymer as a high molecular weight substance, the reaction will not be different between a small molecule and a polymer. In any case, if there are chemical differences between the reactivity of a polymer to the reactivity of a small molecule they are usually the type that makes it difficult to draw conclusions from small molecules to polymers and not the other way around. In the present case it is clear that arylene sulfide is part of the sulfide family and that it undergoes a reaction to become a sulfoxide and in harsher conditions to become a sulfone, like any other sulfide. This was also shown in the SWERN publication where there is no distinction made between arylene examples and any other examples. There is no doubt that one who is skilled in the art will learn from the examples of arylene sulfide oxidation and oxidation of poly arylene sulfide in order to carry out the oxidation reaction in the application. The difference in the substituent features on the sulfur atom will of course be taken into account as part of the prior art in the field but there is nothing new. The proof of this is that the knowledge of the field on the priority date shows that the required oxidation reaction does not require extreme conditions to be carried out in any of these molecules.

I do not understand the way the petitioner arrives at the conclusion that "reactivity of the sulfide intermediate and reactivity of a polyaryl sulfide are completely different and oxidation medium of a polyarylenesulfide is not at all relevant to what is being discussed here. If there is any attributable relevance to patent **761** it would be that it indicates that dichloroacetic acid is not expected to be a good choice for the oxidation of the sulfide intermediate". If this is the case, then it only indicates that dichloroacetic acid is not expected to work for the oxidation of the sulfide intermediate, which is characterized by the presence of strong electron attractive groups to Fipronil, as indeed is also highlighted in the specific literature that deals with the oxidation of the sulfide intermediate.

1. From the reading of the literature and comparing the reaction conditions set forth in 761, I learned that it is possible to oxidize, with high yields and selectivity, sulfides to sulfoxides in a mixture of hydrogen peroxide and dichloroacetic acid, **DCA**[[74]](#footnote-74). Since for the sake of the reaction, some or even a small amount of the polymer will most likely dissolve in the reaction mixture shows that **DCA** acts as a solvent used in this example as well as what I learned from the statement, a mediator of the oxidation process[[75]](#footnote-75). In any case, in my eyes, publication **761** clearly steers the professional in the field in the direction of using **DCA**, I cannot think of even one logical argument based on publication **761** that will sway the professional from using **DCA** based on the contents therein. As I understand, the applicant's argument is totally unsubstantiated and incorrect. [Please recall that this discussion is somewhat theoretical in light of the Australian publication **462**, which was also known to the person skilled in the art before the priority date].

**i. The invention claimed in all the dependant claims is obvious**

1. In section e.2. above, I detailed how each of the dependent claims limits claim 1. The limitations of claim 1 are obtained by combining restrictive details of various elements in the claim's process of oxidation. As I understand it, none of the restrictive elements of claim 1 are novel or unexpected. The petitioner as well, does not attribute novelty or unexpectedness to any of the various combinations of the dependent claims. As I understand it, the combination of claim 1, which has no novelty relative to previous knowledge, with restrictive elements of various dependent claims does not produce in any of the dependent claims a novel invention that has unexpectedness or a discovery beyond the routine steps that a person skilled in the arts would normally do.

**j. Summary and conclusions**

1. In view of the above, my conclusions are, unequivocally, that on the priority date:
	1. The invention claimed in the patent application was primarily described in publication **462** and therefore has no novelty.
	2. The invention was not unexpected in the eyes of a person skilled in the arts, which, in light of the prior knowledge in the field, would have tried to carry out the invention, with a high expectation of success. In other words, the invention was not off the track of which an average skilled person working in that field would have routinely done at the priority date, if said person would have been asked to oxidize a substance from a member of the family of substances **II** to a product of the family of substances **I**. Nor was there any difficulty or obstacle that a skilled person would have to overcome in order to reach the invention. This is true even when disregarding publication **462** and are so much more reinforced in light of publication **462**.

1. A sulfur atom bound to two carbon atoms will be herein called a sulfide or thio-ether or Sulfanyl. Oxidizing the sulfur atom in the sulfide group, which is when an oxygen atom is bound to the sulfur atom, will result in a group that will be herein termed sulfoxide (S=O, sulfinyl). [↑](#footnote-ref-1)
2. “Compendium of Chemical Terminology” Gold Book, International Union of Pure and Applied Chemistry, Version 2.3.3, 2014-02-24, pp. 1048-1049. <http://goldbook.iupac.org/O04362.html> [↑](#footnote-ref-2)
3. “Compendium of Chemical Terminology” Gold Book, International Union of Pure and Applied Chemistry, Version 2.3.3, 2014-02-24, p. 1271; <http://goldbook.iupac.org/R05222.html> [↑](#footnote-ref-3)
4. In my literature survey, I will only include the background that was publically published when the patent was filed, unless otherwise stated. [↑](#footnote-ref-4)
5. See **Kaczorowska’s** article, (appendix 10 to this expert opinion), pages 8317-8324. [↑](#footnote-ref-5)
6. The petitioner in its claims also refers to a number of publications that deal with direct oxidation processes of sulfides (appendices 1, 2, 5, 7 that were attached to the petitioner’s documents). However, these publications are irrelevant to the patent application. [↑](#footnote-ref-6)
7. See **March** (appendix 22 to this expert opinion) [↑](#footnote-ref-7)
8. See **March** (appendix 22 to this expert opinion) [↑](#footnote-ref-8)
9. See modern oxidation methods page 194 (appendix 11 in this expert opinion). [↑](#footnote-ref-9)
10. See **Hussain** (appendix 16 in this expert opinion). [↑](#footnote-ref-10)
11. See **Swern** page 34 (appendix 12 in this expert opinion) [↑](#footnote-ref-11)
12. See **March** (appendix 22 to this expert opinion) [↑](#footnote-ref-12)
13. Please insert here all the places where DCA is used as an intermediary in an oxidation reaction. [↑](#footnote-ref-13)
14. See example in **Hsu** (appendix 24 in this expert opinion) and see also **Searles** (appendix 25 in this expert opinion). [↑](#footnote-ref-14)
15. See **390** (appendix 6 in this expert opinion) and also **760** (appendix 19 in this expert opinion). [↑](#footnote-ref-15)
16. This case is referring to oxidizing thiofene to thiofene oxide, which is comparable to oxidizing a sulfide to a sulfoxide. See **440** (appendix 8 in this expert opinion). See also **761** (appendix 7 to this expert opinion). [↑](#footnote-ref-16)
17. See **Treiber** (appendix 17 to this expert opinion, Table 5 page 7262). [↑](#footnote-ref-17)
18. See **Pandeeswaran** (appendix 23 to this expert opinion). [↑](#footnote-ref-18)
19. See **Swern**, page 34 (appendix 12 to this expert opinion). [↑](#footnote-ref-19)
20. See **Swern**, Table 5 pages 35-36 (appendix 12 to this expert opinion). [↑](#footnote-ref-20)
21. See **Swern**, Table 5 pages 35-36 (appendix 12 to this expert opinion). [↑](#footnote-ref-21)
22. See **372** (appendix 5 in this expert opinion). [↑](#footnote-ref-22)
23. See **Greenspan** (appendix 15 to this expert opinion) [↑](#footnote-ref-23)
24. Ibid, page 907. Aliphatic organic acids are acids that do not have any aromatic groups and included in this category are acetic acid, dichloroacetic acid and others. [↑](#footnote-ref-24)
25. See **896** (appendix 9 to this expert opinion). [↑](#footnote-ref-25)
26. See **372** (appendix 5 to this expert opinion). [↑](#footnote-ref-26)
27. See paragraph 52 of the opposition claims. [↑](#footnote-ref-27)
28. See the **Swern** publication page XXX (appendix 12 of this expert opinion). [↑](#footnote-ref-28)
29. See the **Swern** publication page XXX (appendix 12 of this expert opinion). [↑](#footnote-ref-29)
30. The brackets were added by me for clarification purposes. [↑](#footnote-ref-30)
31. <http://www.merriam-webster.com/dictionary/in%20situ> [↑](#footnote-ref-31)
32. Celsius [↑](#footnote-ref-32)
33. As mentioned above, the claim narrows the previous claims in that **DCA** is oxidized to **DCPA** by an oxidizer listed in claim 1. [↑](#footnote-ref-33)
34. Whether it is made outside or in the reaction vessel (*in situ*, for example, from a reaction between **TFA** and an oxidizing agent). [↑](#footnote-ref-34)
35. “Method according to claim 4 wherein oxidation of the dichloroacetic acid takes place *in situ*” [↑](#footnote-ref-35)
36. Meaning, the oxidation of material from the family of compound **II** to the family of compound **I**. [↑](#footnote-ref-36)
37. What I mean by the term overlap, is at least a partial identity between the elements of the group. In the present case, R3 is defined in **462** as a perhaloalkyl and in the patent application as a -CF3 which is contained in the R1 group. Perhaloalkyl and R2 are defined in 462 as halogens, and in the application they have been defined as halogens or a hydrogen, independently. [↑](#footnote-ref-37)
38. With the necessary changes for R1, R2 and R3 [↑](#footnote-ref-38)
39. See chapter e.1. above. [↑](#footnote-ref-39)
40. The difference between the two families of materials (**I** according to the patent application and **I** in patent application 462) is the definition of the R groups. R1 and R2 in the patent application are halogens or hydrogen and in application 462, R1 and R2 are halogens only. In addition, Also R3 in the patent application is -CF3 and in patent application 462, R3 is broader and includes in addition to -CF3 also other Perhaloalkyl substances. [↑](#footnote-ref-40)
41. The difference between the two families of materials (**II** in the patent application and **IX** in 462) is the definition of the R groups. R1 and R2 in the patent application are halogens or hydrogen and in application 462, R1 and R2 are halogens only. Also R3 in the patent application is -CF3 and in application 462, R3 is broader and includes in addition to -CF3, also other Perhaloalkyls. [↑](#footnote-ref-41)
42. See chapter e.2. above [↑](#footnote-ref-42)
43. Paragraphs 45-47 of the arguments [↑](#footnote-ref-43)
44. See for example publication **462** page 19 lines 4-7 [↑](#footnote-ref-44)
45. See for example publication **462** page 28 lines 20-21 [↑](#footnote-ref-45)
46. See publication **462** page 32 line 14 [↑](#footnote-ref-46)
47. See publication **462** page 32 line 14 [↑](#footnote-ref-47)
48. See publication **462** page 12 lines 21-24 (appendix 4 to this expert opinion). [↑](#footnote-ref-48)
49. See publication **462** page 14 line 1 (appendix 4 to this expert opinion). [↑](#footnote-ref-49)
50. It is important to put here all that we have on this [↑](#footnote-ref-50)
51. Please put here all the publications that describe DCA transforming into DCPA [↑](#footnote-ref-51)
52. See paragraph 22 above [↑](#footnote-ref-52)
53. See publication **462** (appendix 4 to this expert opinion), publication 440 (appendix 8 to this expert opinion and publication **761** (appendix 7 to this expert opinion. [↑](#footnote-ref-53)
54. See publication **670** (appendix 6 to this expert opinion), publication **462** (appendix 4 to this expert opinion and publication **761** (appendix 7 to this expert opinion. [↑](#footnote-ref-54)
55. A series of chemical compounds showing a uniform type of progressive changes in their physical attributes, and they can be represented in a general formula. Each compound is different than the previous one because of the addition of an identical group of atoms. This is called a homologous series. [↑](#footnote-ref-55)
56. See publication **462** (appendix 4 to this expert opinion). [↑](#footnote-ref-56)
57. See **Swern** publication page 10 lines 27-31 (appendix 12 to this expert opinion) [↑](#footnote-ref-57)
58. See slides from the course (appendix 21 to this expert opinion). [↑](#footnote-ref-58)
59. See, for instance, in the patent request itself paragraph 0078 "Even if not previously specified, a person skilled in the art may, using the expertise typical of the sector, vary or replace some of the aspects described above with other technically equivalent ones.". [↑](#footnote-ref-59)
60. See publication **760** page 7 lines 17-19 and also claim 1 and 2 in this publication (appendix 6 to this expert opinion). [↑](#footnote-ref-60)
61. See for instance **Venier** (appendix 18 to this expert opinion). [↑](#footnote-ref-61)
62. See chapter g above. [↑](#footnote-ref-62)
63. See publication **440** (appendix 8 to this expert opinion) and also see publication **462** (appendix 4 to this expert opinion) [↑](#footnote-ref-63)
64. Application WO 760 teaches, therefore, that these oxidizing agents that the researchers tried were found unsuitable and teaches against the use of these compounds. [↑](#footnote-ref-64)
65. The words in brackets and in bold were added by the undersigned to help clarify the material and are not in the original material. [↑](#footnote-ref-65)
66. See publication 440 (appendix 8 to this expert opinion) page 8 lines 21-24 and page 9 lines 1-2. [↑](#footnote-ref-66)
67. See publication **440** (appendix 8 to this expert opinion) page 9 lines 17-21. [↑](#footnote-ref-67)
68. See **Treiber** publication (appendix 17 to this expert opinion). [↑](#footnote-ref-68)
69. See publication **896** page XXX column 2 lines 19-22 (appendix 9 to this expert opinion). We should add whatever we have in this matter [↑](#footnote-ref-69)
70. See the **Swern** publication, Table 5 pages 35-36 (appendix 12 to this expert opinion) [↑](#footnote-ref-70)
71. See the patent application page 4 line 25 till page 5 line 7. [↑](#footnote-ref-71)
72. See paragraph 44 of the arguments [↑](#footnote-ref-72)
73. See publication **761** column 3 lines 56-59 (appendix 7 to this expert opinion) [↑](#footnote-ref-73)
74. See publication **761**, examples 13-16 (appendix 7 to this expert opinion). [↑](#footnote-ref-74)
75. See publication **761**, column 1 lines 53-60 and also column 3 lines 7-11 (appendix 7 to this expert opinion [↑](#footnote-ref-75)