To: BROECKAERT Fabrice; [redacted] ECHA Committee Risk Assessment
Cc: BOWMER Tim; [redacted]
Subject: RE: Adverse Effect Monitoring - Syngenta Data - Pinoxaden

From: BROECKAERT Fabrice
Sent: 02 September 2016 11:44
To: [redacted] <[redacted]@ecpa.eu>; ECHA Committee Risk Assessment <rac@echa.europa.eu>
Cc: BOWMER Tim <Tim.BOWMER@echa.europa.eu>; [redacted] <[redacted]@echa.europa.eu>
Subject: RE: Adverse Effect Monitoring - Syngenta Data - Pinoxaden

Dear [redacted]

Thank you for forwarding this document. I will pass it to the Rapporteurs since we wish this case to be smoothly adopted at the next plenary. If they agree, we will upload it to CIRCA.

Kind regards,
Fabrice

From: [redacted] [mailto:[redacted]@ecpa.eu]
Sent: 02 September 2016 11:36
To: ECHA Committee Risk Assessment <rac@echa.europa.eu>; BROECKAERT Fabrice <Fabrice.BROECKAERT@echa.europa.eu>
Cc: BOWMER Tim <Tim.BOWMER@echa.europa.eu>
Subject: Adverse Effect Monitoring - Syngenta Data - Pinoxaden

Dear Fabrice, Syngenta noted a question raised in the pinoxaden presentation and would like to provide the attached data that shows how they monitor for adverse effects across a wide range of those exposed to formulated products.

The question they feel this could answer of at least add some useful background information is in slide 15

Relevant information to assess respiratory sensitisation of pinoxaden (6) – slide 15

- *Industry informed in their statement that they were **not aware of adverse effects related to** the handling of the **formulated product**.*
- *However, it is uncertain how efficient symptoms from the end users can be monitored by industry*

Syngenta recognise this is very late arriving information but felt it should be offered as a help to the rapporteur and RAC experts understand the systems in place that a modern PPP manufacturing company develops to monitor for potential adverse effects.
Best regards and thanks
[redacted]

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Pinoxaden – Additional Information for the ECHA RAC Meeting of September 14-16th 2016

With reference to the draft slide-set provided by the Rapporteur, Syngenta would like to offer some additional information to address one of the areas of uncertainty highlighted.

Relevant information to assess respiratory sensitisation of pinoxaden (6) – slide 15

- *Industry informed in their statement that they were **not aware of adverse effects related to** the handling of the **formulated product**.*
    - *However, it is uncertain how efficient symptoms from the end users can be monitored by industry*

Syngenta now have details of the number of users of pinoxaden formulations in Europe. The total for Europe is concluded to be approximately 200,000; numbers for the rest of the world are not included but pinoxaden is registered globally, hence the total number of end users will be much higher than this.

Summary of Users of Pinoxaden in Europe

EU region	Countries included	Number of users
South east	BG,CRO,GRE,HU,RO,SLO	11,300
EU central	DE,AT,PL,LT.LV,EE.CZ,SK,CH	Approx. 41,000
EU others	ES,IT,UK/IRE,FI,NO,NL,BE	Approx. 140,000

Syngenta not only maintains detailed records of any adverse health effects reported by the manufacturing workforce but also keeps detailed records of exposure and poisoning incidences on marketed products and has done so for many years. Incident data reported for product users are collected in two different databases. Reports on cases reported in the USA and Canada are collected in the Prosar database, all other cases are reported into the Adverse Health Incident Database (AHI-DB). In addition Syngenta has close contact with various poisons agencies and are informed of any significant incidents reported to them. We are confident that we would be informed of any significant adverse health incidents from any product users. We have only 4 reports of adverse incidents associated with pinoxaden, none of which indicate respiratory effects causally related to pinoxaden exposure. (Appendix 1).

Attached (Appendix 2 and 3) are examples of summaries of medical data on 2 Syngenta active ingredients for information, which illustrate the successful recording of adverse data using these systems.

Appendix 1: Data from the Syngenta Adverse Health Incidents Database

Year	Suspected route of exposure	Description of circumstances	Medical treatment	Causal link	Outcome	Respiratory system	Throat	Severity Grade	Total	Potentially related to respiratory effects
2011	**Inhalation**	The incident took place in January, this year. It was an application with pxn + Adigor. This man wasn't the applicator, he was supervising the application. So he wasn't directly in contact with the products, neither during the mix nor during the application. He was present during 2 applications, both of them the same day. The exposure time was 30 minutes + 20 minutes Symptoms; cough (4 or 5 days). The symptoms were resolved completely after a week. There was no intervention medical. Possible causes: he thinks that it could have been the product or other cause. Causal link: "unrelated"		Unrelated	**Fully Recovered**	yes	**yes**	minor	1	no
2011	**Inhalation**	Telefonical advice of a hospital. Exposition: 6 hours ago. Inhalation and skin, validated. Products: Axial and Primus. Symptoms: dizziness, shortness of breath (dyspnoe), collapse. Recommendaton: symptomatical therapy.						moderate	1	no
2015	**Inhalation**	Telephonic advice of doctor. Patient, adult male, was exposed via inhalation to Traxos while application of the product outdoors. Symptoms: multiple organ failure due to cardiogenic shock. Patient was in rehabilitation in clinic. Case might be due to drug abuse. The situation is unclear and cannot be clarified, because no access to data.	**clinic, rehabilitation**	Insufficient Information	**Pending**	no	**no**	moderate	1	symptoms were most likely caused by drugs
2015	**Inhalation**	Telephonic advice of non-professional Person. Patient adult, exposed to some Drops of axial 50 via Inhalation one day ago at home. Symptoms: None. Recommendation: in case of discomfort, especially inhalative Problems consult doctor. Monitor.	**No**	Open Assessment	**Pending**	no	**no**	none	1	no observed symptoms
									4	

Appendix 2: PIRIMIPHOS-METHYL

Medical Data

IIA 5.9.1 Medical surveillance on manufacturing site personnel

Pirimiphos-methyl is a broad-spectrum organophosphorus insecticide/acaricide introduced in 1970. It has contact and respiratory action. It is used to control a wide range of pests in glasshouse and field crops and for domestic, amenity and public health purposes, including protection of stored grain. Mode of action is by inhibition of cholinesterase enzymes, leading to typical nervous-system effects.

The technical active ingredient is manufactured by Cheminova (recently became FMC) in Denmark. A wide range of commercial formulation types have been developed including emulsifiable concentrates (EC), wettable powders (WP), dusts (DP) and smoke generators (SG), etc. These are now manufactured by Cheminova and also Syngenta sites at Seneffe, Belgium, Paulinia, Brazil and Cartagena, Colombia.

Biological effect monitoring to detect inhibition of cholinesterase enzymes has been carried out on formulation workers handling organophosphorus compounds, according to relevant national requirements.

Within the UK, monitoring, in the form of plasma and later erythrocyte cholinesterase activity measurement, was carried out at legacy ICI site in Yalding, UK from the mid-1960's to 1990. Whilst depressions in cholinesterase activity were seen during this period, the available records do not indicate these were associated with exposure to pirimiphos-methyl. In the late 1980's, with the introduction of the UK Control of Substances Hazardous to Health (COSHH) Regulations, health surveillance for organosphosphate and carbamate workers was re-assessed. The site had instituted better hygiene control measures and increased effort was put into demonstrating their effectiveness by monitoring compliance with occupational hygiene standard (see below).

In June 1990, a new policy on the health surveillance of organophosphate and carbamate workers was produced by the ICI Health Surveillance Committee. On the basis of risk assessment, it was agreed that cholinesterase activity measures will be done under the following circumstances:

- when the oral MLD of the material is less than 500mg/kg **or** the dermal MLD is less than 1000mg/kg.

and

- when the worker has handled the product for at least 7 days in the previous month.

Work with pirimiphos-methyl did not meet the first criterion and so cholinesterase activity monitoring was stopped in 1990. Since 1990 there have been no adverse health effects associated with pirimiphos-methyl reported at Yalding until the site closed in 2003.

The Occupational Health group of Syngenta has maintained a data base of incidents involving chemical exposure of workers since 1983. At the time it was set up it was used to formally record reports of clinical conditions arising during work at our research station (at Jealott's Hill, Berkshire) and our formulation plant (at Yalding, Kent). From 1994 data has been collected from all our manufacturing, formulation and packing sites around the world.

A query of the Syngenta internal database in August 2015 for pirimiphos-methyl produced **zero** records of adverse health effects reported during the manufacture or formulation of pirimiphos-methyl-containing products over a 50 year period.

Additionally, no adverse reactions to pirimiphos-methyl have been reported from ai manufacturing operations within Cheminova.

CONTROL STRATEGY

The principles of good occupational hygiene practice set a clear hierarchy of control which places primacy to removing the hazard or controlling it by engineering or procedural means, before the use of personal protective equipment (PPE) and respiratory protective equipment (RPE).

This hierarchy of control is clearly followed in Syngenta and includes consideration of aspects such as design and construction of the plant, the cleanliness of the workplace and equipment, working practices and personal hygiene.

For exposure to any substance that can be hazardous by ingestion, absorption or inhalation control must be to a standard that eliminates any health effects.

Ingestion: Eating and drinking are forbidden in areas where chemical handling takes place.

Skin contact: The plant design aims to contain, as far as is possible, chemical exposure by use of total or partial enclosure. Suitable PPE is worn by operators where there is potential for skin exposure.

Inhalation: The plant design aims to contain, as far as is possible, chemical exposure by use of total or partial enclosure and appropriate extraction systems. The plant is designed using the Occupational Exposure Limits (OEL) (see below).

ATMOSPHERIC EXPOSURE STANDARD

Occupational Exposure Limits (OELs) are used in pesticide manufacture as a means of monitoring and controlling atmospheric exposure to chemicals during active ingredient synthesis and formulation. The standards are set by the Syngenta OEL Panel as a primary mechanism of control. These are acceptable concentrations in work-place air based on available toxicology data with the application of a suitable safety factor when making the extrapolation from animal data to a human standard.

The OEL Panel considers the toxicology data available from the package of registration studies together with worker experience during the research, development and commercial manufacturing operations. The standard value is kept under review and may be amended in the light of significant new toxicology or hygiene information.

The current **Syngenta OEL** value for pirimiphos-methyl is **3 mg/m^3** for an 8-hour time weighted average (TWA) exposure. This value is based on the no-observed effect level (NOEL) of 0.4 mg/kg bw/day from the 90-day and 2-year feeding studies in rat, assuming a body weight of 70 kg for an adult worker and a shift inhalation volume of 10m^3. The derived value was rounded so as not to imply unwarranted accuracy.

A review of atmospheric monitoring data from Yalding indicates a 99% compliance with 3mg/m^3 in fixed sampling (all products, all work areas) and 90% compliance in personal sampling. Previous reviews generated in 1987 and 1991 showed similar levels of compliance, indicating consistent control. It should be noted that additional protection is provided by routine use of disposable dust masks for discharging operations.

Syngenta has kept detailed records of exposure and poisoning incidences on marketed products for many years. Incident data in Syngenta are collected in two different databases. Reports on cases reported in the USA and Canada are collected in the *Prosar* database, all other cases are reported into the *Adverse Health Incident Database* (AHI-DB).

A review of the exposure incidences of Pirimiphos-Methyl formulations reported between 2004 and 2014 has been conducted and is presented in the tables below. No information was available in the *Prosar* database (USA and Canada).

Within this 11 years period exposure to Pirimiphos-Methyl after occupational, accidental, intentional and uncertain/unknown exposure did almost cause health effects of transient nature with minor severity or below.

In total 78 cases have been reported in this period. 7 (9%) cases were related to intentional misuse. The other incidents were caused by occupational (49 cases, 63%), accidental (19 cases, 24%) and uncertain (3 cases, 4%) exposure.

Exposure happened predominantly via the by inhalation (49%) followed by skin (18%), ingestion (14%) eye (8%) and other (1%) exposure. For the remaining 10% no exposure route was reported.

The majority of reported incidents were of very low severity grade[1] (minor and none), representing 81% of all reported incidents. All remaining incidents were of moderate severity (19%).

Occupational and accidental exposure predominantly happened via inhalation (55%) followed by dermal (22%) exposure, were causing mainly temporary health effects of minor severity grade.

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[1] **Severity Grades:**

NONE (0):	No symptoms or signs related to poisoning
MINOR (1):	Mild, transient and spontaneously resolving symptoms
MODERATE (2):	Pronounced or prolonged symptoms
SEVERE (3):	Severe or life-threatening symptoms
FATAL (4):	Death

Clinical Toxicology Jan 1998, Vol. 36, No. 3: 205–213.

The following summary tables of exposure related to Pirimiphos-Methyl have been compiled from the AHI-DB[2] database for the period 2004-2014:

exposure/severity	none	minor	moderate	severe	fatal	total
occupational	5	34	10	0	0	**49**
accidental	6	12	1	0	0	**19**
intentional	0	3	4	0	0	**7**
uncertain	1	2	0	0	0	**3**
Total	**12**	**51**	**15**	**0**	**0**	**78**

route/severity	none	minor	moderate	severe	fatal	total
Dermal	1	13	0	0	0	**14**
Eye	0	5	1	0	0	**6**
Ingestion	3	5	3	0	0	**11**
Inhalation	7	21	10	0	0	**38**
Other	0	0	1	0	0	**1**
Unknown	1	7	0	0	0	**8**
Total	**12**	**51**	**15**	**0**	**0**	**78**

[2] Countries included in AHI-DB: Albania, India, Algeria, Argentina, Armenia, Australia, Azerbaijan, Belarus, Belgium, Bosnia-Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Cuba, Czech Republic, Denmark, Ecuador, Egypt, El Salvador, Fiji, France, Georgia, Germany, Greece, Guatemala, Hungary, India, Indonesia, Iraq, Ireland, Italy, Japan, Jordan, Kazakhstan, Kenia, Kenya, Korea Republic of, Kosovo, Kuwait, Kyrgyzstan, Lebanon, Lithuania, Macedonia, Malawi, Malaysia, Mauritius, Mexico, Moldova, Morocco, Mozambique, New Zealand, Nicaragua, Oman, Pakistan, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russian Federation, Serbia, Slovakia, Singapore, Slovenia, Spain, Switzerland, Syrian Arab Republic, Taiwan, Tajikistan, Thailand, Turkey, Turkmanistan, Ukraine, United Arab Republic, United Kingdom, USA, Uzbekistan, Venezuela, Vietnam, Yemen, Zimbabwe

APPENDIX 3: DIFENOCONAZOLE

5.9 Medical Data

5.9.1 Medical surveillance on manufacturing plant personnel and monitoring studies.

Difenoconazole (CGA 169374) is a systemic triazole broad-spectrum fungicide for field, fruit and vegetable crops.

The active ingredient has been manufactured in our manufacturing plant at Monthey in Switzerland since 1990 and formulated at 9 Syngenta sites across the world, as well as at a smaller number of 3rd party sites. The typical volume of technical active ingredient manufactured per year is 3000 tonnes.

In 2002, data was sought from all sites handling either the technical active ingredient or formulated product and summarized[3] in a memo of 6th March 2003, confirming that no cases of adverse health effects had been reported. Since 2002, the Occupational Health group of Syngenta has maintained a database of incidents involving chemical exposure of workers. A query of the Syngenta internal database in January 2016 for difenoconazole resulted in **zero** records of adverse health reported from the handling of difenoconazole during synthesis and formulation activities.

CONTROL STRATEGY

The principles of good occupational hygiene practice set a clear hierarchy of control which places primacy to removing the hazard or controlling it by engineering or procedural means, before the use of personal protective equipment (PPE) and respiratory protective equipment (RPE).

This hierarchy of control is clearly followed in Syngenta and includes consideration of aspects such as design and construction of the plant, the cleanliness of the workplace and equipment, working practices and personal hygiene.

For exposure to any substance that can be hazardous by ingestion, absorption or inhalation control must be to a standard that eliminates any health effects.

Ingestion: Eating and drinking are forbidden in areas where chemical handling takes place.

Skin contact: The plant design aims to contain, as far as is possible, chemical exposure by use of total or partial enclosure. Suitable PPE is worn by operators where there is potential for skin exposure.

Inhalation: The plant design aims to contain, as far as is possible, chemical exposure by use of total or partial enclosure and appropriate extraction systems. The plant is designed using the Occupational Exposure Limits (OEL) (see below).

ATMOSPHERIC EXPOSURE STANDARD

Occupational Exposure Limits (OELs) are used in pesticide manufacture as a means of monitoring and controlling atmospheric exposure to chemicals during active ingredient synthesis and formulation. The standards are set by the Syngenta OEL Panel as a primary mechanism of control. These are acceptable concentrations in work-place air based on available toxicology data with the application of a suitable safety factor when making the extrapolation from animal data to a human standard.

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[3] Adverse Health Effects from Difenoconazole Synthesis and Formulation, 6th March 2003 K.J. Ledgerwood Memo.

The OEL Panel considers the toxicology data available from the package of registration studies together with worker experience during the research, development and commercial manufacturing operations. The standard value is kept under review and may be amended in the light of significant new toxicology or hygiene information.

The current **Syngenta OEL** for difenoconazole is based on the no-observed effect level (NOEL) of 3.4 mg/kg bw/day from the 1-year feeding study in dog, assuming a body weight of 70 kg for an adult worker and a shift inhalation volume of $10m^3$. The derived value would be rounded down so as not to imply unwarranted accuracy. In this case, the limit is reduced further to **5 mg/m³** for an 8-hour time weighted average (TWA) exposure, equivalent to the agreed Syngenta maximum concentration for relatively non-toxic 'nuisance dusts'.

In conclusion, difenoconazole has been handled in large quantities for over 25 years, at a number of sites and with the use of appropriate control strategies, no adverse health effects associated with the material have been reported in the workforce.

Syngenta has kept detailed records of exposure and poisoning incidences on marketed products for many years. Incident data in Syngenta are collected in two different databases. Reports on cases reported in the USA and Canada are collected in the *Prosar* database, all other cases are reported into the *Adverse Health Incident Database* (AHI-DB).

A review of the exposure incidences of Difenoconazole formulations reported between 2004 and 2014 has been conducted and is presented in the tables below.

Within this 11 years period exposure to Difenoconazole after occupational, accidental, intentional and uncertain/unknown exposure did almost cause health effects of transient nature of almost minor severity or below.

In total 187 cases have been reported in this period. 50 cases (27%) were related to intentional misuse. The other incidents were caused by occupational (69 cases, 37%), accidental (63 cases, 34%) and uncertain (5 cases, 3%) exposure.

Exposure happened predominantly via ingestion (55%) and dermal exposure (18%) followed by inhalation (14%), unknown (9%), eye (3%) and other (1%) exposure.

The majority of reported incidents were of very low severity grade[4] (minor and none), representing 90% of all reported incidents. Incidents assigned to fatal and severe severity grades representing 0.5% each. Other cases were assigned to moderate (9%) or none (27%) severity grade.

Highest severity grade (fatal) was reported for a single case caused by deliberate self-harm. The person affected ingested in addition also other products. It was his third attempt to commit suicide. The second highest severity grade (severe) was assigned to another case of deliberate self-harm. The

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[4] **Severity Grades:**

NONE (0):	No symptoms or signs related to poisoning
MINOR (1):	Mild, transient and spontaneously resolving symptoms
MODERATE (2):	Pronounced or prolonged symptoms
SEVERE (3):	Severe or life-threatening symptoms
FATAL (4):	Death

Clinical Toxicology Jan 1998, Vol. 36, No. 3: 205–213.

patient ingested one liter of the product similar to the case reported above together with another pesticide and alcohol. After medical treatment the patient recovered completely without remaining symptoms. Based on the reported details of both cases the fatal outcome of one of the incidents cannot be related to the Difenconazole containing product.

Occupational and accidental exposure cases happened predominantly via ingestion (41% of occupational and accidental exposure cases), followed by dermal exposure (26% of occupational and accidental exposure cases), inhalation (19% of occupational and accidental exposure cases), unknown (8% of occupational and accidental exposure cases), eye (5% of occupational and accidental exposure cases) and other (2% of occupational and accidental exposure cases) exposure.

The tables below are summarizing exposure cases related to Difenoconazole compiled from the *AHI-DB*[5] and *PROSAR* (USA/Canada) databases for the period 2004-2014 (data provided as number of reports received).

exposure/severity	none	minor	moderate	severe	fatal	total
occupational	11	50	8	0	0	**69**
accidental	31	28	4	0	0	**63**
intentional	7	38	3	1	1	**50**
uncertain	1	2	2	0	0	**5**
Total	**50**	**118**	17	**1**	**1**	**187**

route/severity	none	minor	moderate	severe	fatal	total
Dermal	4	23	7	0	0	**34**
Eye	1	4	1	0	0	**6**
Ingestion	31	64	5	1	1	**102**
Inhalation	1	22	3	1	0	**27**
Other	0	2	0	0	0	**2**
Unknown	12	3	1	0	0	**16**
Total	**49**	**118**	17	**2**	**1**	**187**

[5] Countries included in AHI-DB: Albania, India, Algeria, Argentina, Armenia, Australia, Azerbaijan, Belarus, Belgium, Bosnia-Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Cuba, Czech Republic, Denmark, Ecuador, Egypt, El Salvador, Fiji, France, Georgia, Germany, Greece, Guatemala, Hungary, India, Indonesia, Iraq, Ireland, Italy, Japan, Jordan, Kazakhstan, Kenia, Kenya, Korea Republic of, Kosovo, Kuwait, Kyrgyzstan, Lebanon, Lithuania, Macedonia, Malawi, Malaysia, Mauritius, Mexico, Moldova, Morocco, Mozambique, New Zealand, Nicaragua, Oman, Pakistan, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russian Federation, Serbia, Slovakia, Singapore, Slovenia, Spain, Switzerland, Syrian Arab Republic, Taiwan, Tajikistan, Thailand, Turkey, Turkmanistan, Ukraine, United Arab Republic, United Kingdom, USA, Uzbekistan, Venezuela, Vietnam, Yemen, Zimbabwe