DRAFT REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: A20607B

Product name(s): Vibrance SB

Chemical active substances:

Fludioxonil, 22.5 g/L
Metalaxyl-M, 14.4 g/L
Sedaxane, 15 g/L

~~United Kingdom~~

Great Britain (GB)

NATIONAL ASSESSMENT

~~(Renewal of authorisation)~~

Submitted to support Article 7 amendment of approval of Metalaxyl-M in GB

Applicant: Syngenta

Submission date: 21/10/2021

Finalisation date: 31/01/2024

Version history

When	What
October 2021	Applicant submission to support amendment of approval under Article 7 of retained Regulation (EC) No 1107/2009
December 2023	HSE (GB) assessment added in green boxes

This is an application from Syngenta for the renewal of VIBRANCE SB (A20607B) under Article 43 of Regulation (EC) No. 1107/2009 following the renewal of EU approval of the active substance Metalaxyl-M.

No equivalence assessment is required.

This application follows the data requirements for the active substance laid down in Regulation (EU) No. 544/2011 and the data requirements for the plant protection product laid down in Regulation (EU) No. 545/2011, also called 'old' data requirements. Metalaxyl-M is an 'AIR-2' substance which approval has been renewed in accordance with Regulation (EU) No 1141/2010, therefore Regulations (EU) No 283/2013 and (EU) No 284/2013 are not applicable to the renewal of authorizations for Metalaxyl-M-containing plant protection products (derogation by Commission Regulation (EU) No 2015/1475; further details in the guidance document SANTE/11509/2013 rev. 5.2).

Following the renewal of EU approval of the active substance Metalaxyl-M, the submission for the product renewal of VIBRANCE SB (A20607B) was made by 01 September 2020, in accordance with Article 43 of Regulation (EC) No 1107/2009.
All data relied on are provided with this application. The reference lists at Appendix 1 of dRR Part B Sections 1-10 define the data owner and data access. Data protection is a national concern and is addressed in Part A, Appendix 4.

The guidance on Renewal of Authorization according to Art 43 (SANCO/2010/13170 rev 14) requests that within the dRR 'changes to the risk assessment are highlighted'. This is the first submission of VIBRANCE SB (A20607B) in the dRR format of April 2015, consequently all of the summary text is previously unreviewed and should be considered as 'changed'. To facilitate the review, Syngenta has highlighted the summaries of reports not previously reviewed by the zRMS in yellow.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	The applicant, Syngenta Crop Protection AG, submitted this application to amend the conditions of approval of metalaxyl-M in accordance to Article 7 of Regulation 1107/2009 in Great Britain (GB). On the 5 May 2020 the Commission Implementing Regulation (EU) 2020/617 renewing the approval of the active substance metalaxyl-M, and restricting the use of seed treat-

ed with a plant protection product containing it to be sown only in greenhouses, was published[1]. The renewal of metalaxyl-M applies since 1 June 2020. Since this was before UK withdrawal from the EU, the Commission Implementing Regulation for the renewal of metalaxyl-M applies direct in GB.

Two representative formulations were considered in the renewal of approval for metalaxyl-M, 'Apron XL' (A9642C) and 'Ridomil Gold Mz'/68 WG Fubol Gold' (A9651D). For this Article 7 amendment application in GB, two different formulations have been considered. The formulation 'Vibrance SB' (A20607B) containing 14.4 g/L metalaxyl-M, 22.5 g/L fludioxonil and 15.0
g/L sedaxane to support the field seed treatment use on sugar and fodder beet, and the formulation 'Wakil XL' (A9873C) containing 169.6 g/Kg metalaxyl-M, 100 g/Kg cymoxanil and 50 g/Kg fludioxonil) to support
the field seed treatment use on peas (vining) are the basis of this Article 7 application for metalaxyl-M to GB.

The applicant has re-submitted the draft registration reports prepared for the product renewals of 'Vibrance SB' and 'Wakil XL' under Article 43 of Regulation No 1107/2009 following the renewal of approval of the active substance metalaxyl-M. The information and data submitted within these draft registration reports have been considered previously by HSE for the applications for authorisation of a new product under Article 33 of Regulation No 1107/2009. Where relevant, re-evaluation of data or information has not occurred where studies have been performed in accordance with the current requirements and the results have been deemed acceptable.

This draft registration report has been provided by the applicant, where required, comments have been inserted in green boxes by HSE or the text amended by the HSE in green (applicant's text has been struck through in green where necessary).

HSE notes that the product authorisations for 'Vibrance SB' and 'Wakil XL' were withdrawn in GB by the applicant. This was based on the approval restriction provided for in Commission Implementing Regulation (EU) 2020/617 that only the treatment of seeds intended to be sown in greenhouses may be authorised. Since all authorised GB uses of 'Vibrance SB' and 'Wakil XL' products are on seeds which are direct drilled in the field, these products do not comply with the restriction and therefore could not be renewed under Article 43 of Regulation No 1107/2009. HSE notes that no authorisation for 'Vibrance SB' or 'Wakil XL' is sought within this Article 7 amendment application. Therefore, HSE has only considered the information presented in the draft registration reports that relate to metalaxyl-M. For a future GB authorisation of these products a separate application would be required with a full evaluation of the data and information for all active substances present in the formulation.

Note that as of 1st January 2024, The Retained EU Law (Revocation and Reform) Act 2023 has taken effect and retained EU law are now known as assimilated law. As this assessment has been prepared prior to the Retained EU Law Act taking effect, assess-

[1] Commission Implementing Regulation (EU) 2020/617 of 5 May 2020 renewing the approval of the active substance metalaxyl-M, and restricting the use of seeds treated with plant protection products containing it, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending the Annex to Commission Implementing Regulation (EU) No 540/2011

	ment may still refer to “retained” regulation as opposed to “assimilated”.

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6 Mammalian Toxicology (KCP 7)

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The product Vibrance SB (A20607B) has been evaluated as a representative use for the Article 7 evaluation of the active substance metalaxyl-M. Vibrance SB was previously authorised under an Article 33 Following Zonal application. Where relevant, re-evaluation of data to address human health hazard classification or dermal absorption values have not occurred. Where possible the conclusions from the Following Zonal evaluation have been confirmed under this Article 7 evaluation. For the groundwater metabolite relevance assessment and dermal absorption values, only the active substance metalaxyl-M has been evaluated. Combined toxicity between active substances present in Vibrance SB (A20607B) has not been evaluated under the Article 7 evaluation, only the toxicity of metalaxyl-M has been considered.

6.1 Summary

Table 6.1-1: Information on A20607B / Vibrance SB*

Product name and code	A20607B / Vibrance SB
Formulation type	Flowable concentrate for seed treatment (FS)
Active substances (incl. content)	Fludioxonil : 22.5g/L Metalaxyl-M : 14.4g/L Sedaxane : 15g/L
Function	Fungicide
Product already evaluated as the 'representative formulation' during the approval of the active substances	No
Product previously evaluated in another MS according to Uniform Principles	Yes (in izRMS NL since 01/02/2018, Authorization No 15544 N)

* Information on the detailed composition of A20607B / Vibrance SB can be found in the confidential dRR Part C.

Justified proposals for classification and labelling

According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification and labelling with regard to toxicological data is proposed for the preparation:

Table 6.1-2: Justified proposals for classification and labelling for A20607B / Vibrance SB according to Regulation (EC) No 1272/2008

Hazard class(es), categories	n/a
Hazard pictograms or Code(s) for hazard pictogram(s)	n/a
Signal word	n/a
Hazard statement(s)	n/a
Precautionary statement(s)	n/a
Additional labelling phrases	EUH401 To avoid risks to human health and the environment, comply with the instructions for use. EUH208 Contains 1,2-benzisothiazol-3-one. May produce an allergic reaction

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for A20607B

	Result	PPE / Risk mitigation measures
Operators	Acceptable	Gloves, coverall, half-face mask and safety spectacles
Workers	Acceptable	Gloves when loading the hopper
Residents	Not applicable	Not applicable
Bystanders	Not applicable	Not applicable

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in Table 6.1-3 are applied.

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and residents/bystanders is presented in the following table.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY

Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: Based on the information available, the formulated product A20607B meets the criteria for classification for the following human health hazard in accordance with Regulation 1272/2008 (CLP): **Carcinogenicity Category 2 (H351)** The following label elements should be used with respect to human health:

Hazard class(es), categories	**Carc. Cat. 2; H351**
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS08
Signal word	Warning
Hazard statement(s)	Suspected of causing cancer

Precautionary Statements triggered by human health hazard classification P280 Wear protective gloves/protctive clothing/eye protection/face protection P308 + P313 IF exposed or concerned: Get medical advice/attention.	
EUH208	'Contains 1,2-benzisothiazol-3-one. May produce an allergic reaction.'

In addition to the human health hazard classifications, the label needs to include the additional labelling EUH208 'Contains 1,2-benzisothiazol-3-one. May produce an allergic reaction.' (See dRR Part C for details).

No other classification for human health hazards is required based on the submitted information and in accordance with Regulation 1272/2008.

Table 6.1-4 Critical uses and overall conclusion of exposure assessment

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, resident or bystander exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind **(incl. application technique *****	**Max. number (min. interval between applications)** **a) per use** **b) per crop/ season**	**Max. application rate kg as/tonne seed** **1) Fludioxonil** **2) Metalaxyl-M** **3) Sedaxane**	**Max. application rate g a.s./ha** **1) Fludioxonil** **2) Metalaxyl-M** **3) Sedaxane**			**Operator**	**Worker**	**Residents**	**Bystander**
1	Sugar beet (BBCH 00)	I	Treatment of seeds	1 ; 1	1) 0.312 2) 0.200 3) 0.208	1) 0.97 2) 0.62 3) 0.65	n/a	critical gap for operator [Seed-TROPEX sugar beet treatment study data (75th percentile)] and worker [Seed-TROPEX maize sowing study data (75th percentile)]				

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1

** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application

*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Explanation for column 10 "Acceptability of exposure assessment"

A	Exposure acceptable without PPE / risk mitigation measures
R	Further refinement and/or risk mitigation measures required
N	Exposure not acceptable/ Evaluation not possible

Data gaps

Data gaps should be listed in the summary to give an overview (especially for cMS).

Noticed data gaps are:

None

6.2 Toxicological Information on Active Substances

Information regarding classification of the active substances and on EU endpoints and critical areas of concern identified during the EU review are given in Table 6.2-1.

Table 6.2-1: Information on active substances

	Sedaxane	**Fludioxonil**	**Metalaxyl-M**
Common Name	Sedaxane	Fludioxonil	Metalaxyl-M
CAS-No.	874967-67-6	131341-86-1	70630-17-0
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	**Hazard classes (s), categories:** n/a **Code(s) for hazard pictogram(s):** n/a **Signal word:** n/a **Hazard statement(s):** n/a **Precautionary statement(s):** n/a	**Hazard classes (s), categories:** n/a **Code(s) for hazard pictogram(s):** n/a **Signal word:** n/a **Hazard statement(s):** n/a **Precautionary statement(s):** n/a	**Hazard classes (s), categories:** Acute toxicity Category 4, H302 Serious eye damage Category 1, H318 **Code(s) for hazard pictogram(s):** GHS05, GHS07 **Signal word:** Danger **Hazard statement(s):** H302 Harmful if swallowed. H318 Causes serious eye damage. **Precautionary statement(s):** **Prevention:** P264 Wash skin thoroughly after handling. P270 Do not eat, drink or smoke when using this product. P280 Wear eye protection/ face protection. **Response:** P301 + P312 + P330 IF SWALLOWED: Call a POISON CENTER/doctor if you feel unwell. Rinse mouth. P305 + P351 + P338 + P310 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a POISON CENTER/doctor. **Disposal:** P501 Dispose of contents/ container to an approved waste disposal plant.
Additional C&L proposal	n/a	n/a	This substance/mixture contains no components considered to be either persistent, bioaccumulative and toxic (PBT), or very

	Sedaxane	Fludioxonil	Metalaxyl-M
			persistent and very bioaccumulative (vPvB) at levels of 0.1% or higher.
Agreed EU endpoints			
AOEL systemic	0.28 mg/kg bw/d (corrected for 87-89% oral absorption)	0.59 mg/kg bw/d (corrected for 80% oral absorption)	0.08 mg/kg bw/d (corrected for > 80% oral absorption)
Reference	EFSA Journal 2013;11(1):3057	EFSA Scientific Report (2007) 110, 1-85, Conclusion on the peer review of fludioxonil	EFSA Journal 2015;13(3):3999
Conditions to take into account/critical areas of concern with regard to toxicology			
Review Report/EFSA Conclusion for active substance	An issue is listed as a critical area of concern where there is enough information available to perform an assessment for the representative uses in line with the Uniform Principles of Annex VI to Directive 91/414/EEC, and where this assessment does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment. An issue is also listed as a critical area of concern where the assessment at a higher tier level could not be finalised due to a lack of information, and where the assessment performed at the lower tier level does not permit to conclude that for at least one of the representative uses it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater or any unacceptable influence on the environment. 2. On the basis of the available data, a high long-term risk was identified for granivorous birds and granivorous mammals.	• The risk to fish and aquatic invertebrates is high and risk mitigation measures are required for the foliar use in vine. • Based on the available information, soil photolysis metabolites CGA 339833 and CGA 192155 (relevant for foliar spray use only) have the potential to leach to groundwater above the trigger of 0.1 µg/L under vulnerable conditions (to be confirmed by new modelling). A full assessment of the toxicological relevance of these metabolites has not been performed in line with the Guidance document.	An issue is also listed as a critical area of concern the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009. *"The technical specification is not supported by the toxicological assessment due to one relevant impurity CGA226048 that has been shown to be potentially clastogenic and that was not tested at appropriate levels in the toxicological studies."* An on-going EU evaluation is currently being finalised by the active substance RMS Belgium under Article 7 (Application to amend the conditions of approval /Submission of documentation 17th July 2019) showing that impurity CGA226048 (2-[(2,6-dimethyl-phenyl)-(2- methoxyacetyl)-amino]-propionic acid 1-methoxycarbonyl-ethyl ester) is non-genotoxic. Studies demonstrating the lack of clastogenic potential of CGA226048 are submitted here for transparency. Based on the studies' results the maximum limit for CGA226048 of 0.18 g/kg, as currently set in the Metalaxyl-M approval regulation, can be removed as they confirm that the impurity is devoid of genotoxic poten-

	Sedaxane	Fludioxonil	Metalaxyl-M
	3. The relevant groundwater metabolite CSCD465008 exceeds the parametric drinking water limit of 0.1 µg/L in all pertinent groundwater scenarios.		tial. This area of concern has been fully addressed and full summaries of these studies are described in detail in Appendix 2, A 2.11.3 and A 2.11.4). **Reference** KCA 5.4.2, [redacted], 2015 KCA 5.4.2, [redacted], 2017

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY

Name of authority	**HSE Chemicals Regulation Division (CRD)**

Reviewer's comments

Toxicology:

Toxicological information on active substances contained within A20607B.

Metalaxyl-M

The information relating to the human health hazard classification of the active substance metalaxyl-M, as presented in Table 6.2-1 is correct in accordance with the GB mandatory classification of metalaxyl-M[1] and Annex VI of CLP.

The information presented in Table 6.2-1 with regards to toxicological reference values is correct in accordance with the agreed values for metalaxyl-M (EFSA Journal 2015;13(3):3999).

For the sake of clarity, the correct classification and agreed reference values for metalaxyl-M are as follows:

Metalaxyl-M (1.4% in product) (EFSA Journal 2015;13(3):3999)

Classification	Acute oral toxicity Category 4; H302, Serious eye damage Category 1; H318; EU CLH and GB MCL (mandatory classification)'				
AOEL	0.08 mg/kg bw/d	NOAEL = 8 mg/kg bw/d	AF= 100	Dog RDT studies (90-day, 6-month, 1 &2-years)	Increases in liver weight and AP and ALT levels; anaemia
ADI	0.08 mg/kg bw/d	NOAEL = 8 mg/kg bw/d	AF= 100	Dog RDT studies (90-day, 6-month, 1 &2-years)	Increases in liver weight and AP and ALT levels; anaemia
ARfD	0.5 mg/kg bw	NOAEL = 50 mg/kg bw/d	AF= 100	Rat Develop-mental study	Mortality, clinical signs and decrease in bw gain
AAOEL	N/A	N/A	N/A	N/A	N/A

[1] The retained CLP Regulation (EU) No. 1272/2008 as amended for Great Britain.

Sedaxane

The information relating to the human health hazard classification of the active substance sedaxane, as presented in Table 6.2-1 is incorrect in accordance with the GB mandatory classification Technical Report of sedaxane (June 2021)[1] and Annex VI of CLP.

The information presented in Table 6.2-1 with regards to toxicological reference values is correct in accordance with the agreed values for sedaxane (EFSA Journal 2013;11(1):3057).

For the sake of clarity, the correct classification and agreed reference values for sedaxane are as follows:

Sedaxane (1.45% in product) (EFSA Journal 2013;11(1):3057)

Classification	Carc. 2; H351 (Suspected of causing cancer); EU CLH and GB MCL (mandatory classification)				
AOEL	0.28 mg/kg bw/d	NOAEL = 28 mg/kg bw/d	AF= 100	Rat 90-day study	Liver (increased weight), reduced foregrip strength (females)
ADI	0.11 mg/kg bw/d	NOAEL = 11 mg/kg bw/d	AF= 100	Rat 2-year study	Liver (hypertrophy, increased weight)/ thyroid follicular cell hypertrophy, baso-philia
ARfD	0.3 mg/kg bw	NOAEL = 30 mg/kg bw/d	AF= 100	Rat Acute neurotoxicity study	Reduced locomotor activity, decreased body weight, body weight gain, food consumption
AAOEL	N/A	N/A	N/A	N/A	N/A

[1] The retained CLP Regulation (EU) No. 1272/2008 as amended for Great Britain.

Fludioxonil

The information relating to the human health hazard classification of the active substance fludioxonil, as presented in Table 6.2-1 is correct in accordance with the GB mandatory classification of fludioxonil[1] and Annex VI of CLP.

The information presented in Table 6.2-1 with regards to toxicological reference values is correct in accordance with the agreed values for fludioxonil (EFSA Journal 2015;13(3):3999).

For the sake of clarity, the correct classification and agreed reference values for fludioxonil are as follows:

Fludioxonil (2.2% in product) (EFSA Scientific Report (2007) 110, 1-85, Conclusion on the peer review of fludioxonil)

Classification	Not classified; EU CLH and GB MCL (mandatory classification)'

AOEL	0.59 mg/kg bw/d	NOAEL = 58.5 mg/kg bw/d	AF= 100	Dog RDT studies (90-day)	Liver; increased weight, hepatocyte hypertrophy, bile duct proliferation
ADI	0.37 mg/kg bw/d	NOAEL = 37 mg/kg bw/d	AF= 100	Rat 2-years	Liver; increased weight, hepatocyte hypertrophy, bile duct proliferation Kidney; increased weight, nephropathy
ARfD	N/A	N/A	N/A	N/A	N/A
AAOEL	N/A	N/A	N/A	N/A	N/A

[1] The retained CLP Regulation (EU) No. 1272/2008 as amended for Great Britain.

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for A20607B / Vibrance SB is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant proposes to meet the data requirements for acute toxicity (oral, dermal and inhalation), skin and eye irritation and skin sensitisation using studies previously evaluated by HSE. The studies were accepted and evaluated during the following zonal application. Summaries of the studies and confirmation of the conclusions from their evaluation can be found in Appendix 2 of this document. Based on the information available, the formulated product A20607B does not meet the criteria for classification for any acute human health hazard in accordance with Regulation 1272/2008 (CLP). The product contains the active sedaxane. Sedaxane is classified in Category 2 for carcinogenicity in accordance with the GB MCL Technical Report (2021). Sedaxane is present at 15 g/L or 1.45 % w/w in the product. In accordance with Regulation 1272/2008 (CLP), the generic concentration limit is ≥ 1 %; **therefore the product should be classified for Carc. Cat. 2, H351**.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for A20607B / Vibrance SB

Type of test, species, model system (Guideline)	Result	ATE & Additivity Calculation Result	Acceptability	Classification[1] (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (OECD 425)	> 5000 mg/kg bw	24671.05 mg/kg Not classified	Yes	None	Petus–Árpásy M, 2015
LD_{50} dermal, rat (OECD 402)	> 5000 mg/kg bw	>2000 mg/kg Not classified	Yes	None	Petus–Árpásy M, 2015
LC_{50} inhalation, rat (OECD 403)	6.1 mg/L air	>5mg/L Not classified	Yes	None	[redacted], 2015
Skin irritation, rabbit (OECD 404)	Non-irritant	Not irritant Not classified	Yes	None	[redacted], 2015
Eye irritation, rabbit (OECD 405)	Mild irritant.	Eye irritant Category 2	Yes	None	[redacted], 2015
Skin sensitisation, mouse (OECD 429, LLNA)	Non-sensitising	Not a skin sensitizer Not classfied	Yes	None	[redacted], 2015
Supplementary studies for combinations of plant protection products	No data – not required				

[1] Proposed acute toxicity classifications are based on A20607B study results.

Although the classification of this A20607B formulation has been performed using the additivity calculation as indicated in the CLP Guidance to Regulation (EC) No 1272/2008, that ATE calculations result in a more conservative approach. However, Syngenta has also conducted acute toxicity studies on this formulation as at the time of the initial registration as these studies were required for registration in the EU. Where classification proposals have varied between the ATE calculation approach and the animal data generated it is Syngenta's approach to base the product classification on the animal data, in accordance with CLP guidance.

Table 6.3-2: Additional toxicological information relevant for classification/labelling of A20607B / Vibrance SB

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of active substance(s) (relevant for classification of product)	Fludioxonil (>= 1 - < 2.5% (w/w))	Hazard statement n/a	Regulation (EC) 1272/2008 as amended	Hazard statements n/a
	Sedaxane (>= 1 - < 2.5% (w/w))	Hazard statement n/a		
	Metalaxyl-M (>= 1 - < 3% (w/w))	Hazard statements Acute Tox 4; H302 Eye Dam. 1; H318		
Toxicological properties of non-active	1,2-benzisothiazol-	Hazard statements Acute Tox. 4; H302		

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
substance(s) (relevant for classification of product)	3(2H)-one (CAS No. 2634-33-5, (>= 0.025 - < 0.05% (w/w))*	Skin Irrit. 2; H315 Eye Dam. 1; H318 Skin Sens. 1; H317		
	Bronopol (INN) (CAS No. 52-51-7) (>= 0.025 - < 0.1% (w/w))*	Hazard statements Acute Tox. 4; H302 Acute Tox. 4; H312 Skin Irrit. 2; H315 Eye Dam. 1; H318 STOT SE 3; H335		
Further toxicological information	No data – not required			

* Please use concentration range or concentration limit (e.g. 1-10% or > 1%) as provided in MSDS.

6.4 Toxicological Evaluation of Groundwater Metabolites

The following data on metabolites CSCD465008 with the potential to reach the groundwater in concentrations above 0.1 µg/L and requiring relevance assessment were submitted. Note that the relevance assessment of the metabolites CSCD465008 are reported in Part B 10.

There are not relevant metabolites for fludioxonil. The PEC_{GW} for metabolites of metalaxyl-M (NOA409045, CGA67868 and SYN546520) are all below 0.1 µg/L. The PEC_{GW} for the metabolites of sedaxane (CSAA798670 and CSCD728931) are all below 0.1 µg/L. Therefore, no data is required to demonstrate the non-relevance of these metabolites.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: No metabolites of metalaxyl-M are predicted to occur in groundwater at concentrations above 0.1 µg/L. Assessment of the relevance of these metabolites according to the stepwise procedure of the guidance document SANCO 221/2000 Rev 11; 21/10/2021 is reported in dRR Part B 10. No metabolites were found to be relevant.

6.4.1 CSCD465008

An overview of the results of the accepted toxicological studies for groundwater metabolite CSCD465008 is given in the following table. The genotoxicity studies, the acute oral test and the 28-day dietary study have been considered within the EU peer review process for sedaxane. The 90-day dietary study and the developmental toxicity in rabbits have been considered within the EU peer review process for fluxapyroxad (studies sponsored by BASF and now co-owned by Syngenta). Consequently full summaries of these studies are not provided in detail in Appendix 2 (Other/Special Studies).

Table 6.4-1: Summary of the results of toxicity studies for CSCD465008

Type of test, species (Guideline)	Result	Acceptability	Reference*
Bacterial Reverse Mutation	Negative	Yes / No / Supplementary	[redacted], 2008*
In Vitro Cytogenetics	Negative	Yes / No / Supplementary	[redacted], 2008*
Mammalian cell gene mutation (mouse lymphoma)	Negative	Yes / No / Supplementary	[redacted], 2008*
Acute Oral	LD_{50} > 2000mg/kg	Yes / No / Supplementary	[redacted], 2008*
28-day dietary toxicity in the rat	NOAEL > 1000mg/kg bw/day	Yes / No / Supplementary	[redacted], 2008*
90-day dietary toxicity in the rat	NOAEL > 958/929mg/kg bw/day in ♂/♀	Yes / No / Supplementary	[redacted], 2009*
Developmental toxicity in rabbits	Maternal NOAEL = 300mg/kg/day Maternal LOAEL = 1000mg/kg bw/day based on increased mortality and abortions Fetal NOAEL = >1000mg/kg/day	Yes / No / Supplementary	[redacted], 2009*

* indicates that a study was reviewed at EU level

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in A20607B are presented in the following table.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: Under the Article 7 evaluation of metalaxyl-M, the product Vibrance SB (A20607B) has been evaluated as a representative use. As such, only the dermal absorption of metalaxyl-M has been evaluated. The applicant proposes to meet the data requirements for dermal absorption by application of default dermal absorption values in accordance with Section 6.1 of the EFSA guidance on dermal absorption (2017). A20607B is a flowable concentrate for seed treatment (FS); this formulation type falls under the formulation category of 'Water-based/dispersed'. Therefore, as the active substance is present at <5% (in the concentrate), the default values of 50% for the concentrate is applicable. As the product is to be applied only as a concentrate, a dermal absorption value for a dilution is not required. The finalised dermal absorption values to be applied to A20607B are summarised below:

	Metalaxyl-M	
	Value (%)	**Reference**
Concentrate	50	Default values for FS formulation (EFSA Journal 2017; 15(6):4873)
Dilution	N/A	N/A

Table 6.5-1: Dermal absorption rates for active substances in A20607B

	Fludioxonil		**Metalaxyl-M**		**Sedaxane**	
	Value	**Reference**	**Value**	**Reference**	**Value**	**Reference**
Concentrate	50%	Default value – EFSA Guidance on Dermal Absorption. No study data	50%	Default value – EFSA Guidance on Dermal Absorption. No study data	50%	Default value – EFSA Guidance on Dermal Absorption. No study data
Dilution	N/A		N/A		N/A	

6.5.1 Justification for proposed values - fludioxonil

No data on dermal absorption for fludioxonil in A20607B is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-2: Default dermal absorption rates for fludioxonil

	Value	Justification for value	Acceptability of justification
Concentrate	50 %	Active ingredient present below 5% in formulation	Yes / No / Supplementary
Dilution	N/A	Used as concentrate only	Yes / No / Supplementary

6.5.2 Justification for proposed values – metalaxyl-M

No data on dermal absorption for metalaxyl-M in A20607B is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-3: Default dermal absorption rates for metalaxyl-M

	Value	Justification for value	Acceptability of justification
Concentrate	50 %	Active ingredient present below 5% in formulation	Yes
Dilution	N/A	Used as concentrate only	Yes

6.5.3 Justification for proposed values - sedaxane

No data on dermal absorption for sedaxane in A20607B is available. Justifications for default values according to Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873) are presented in the following table.

Table 6.5-4: Default dermal absorption rates for sedaxane

	Value	Justification for value	Acceptability of justification
Concentrate	50 %	Active ingredient present below 5% in formulation	Yes / No / Supplementary
Dilution	N/A	Used as concentrate only	Yes / No / Supplementary

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Table 6.6-1: Product information and toxicological reference values used for exposure assessment

Product name and code	A20607B		
Formulation type	Flowable concentrate for seed treatment (FS)		
Category	Fungicide		
Active substance (incl. content)	**Fludioxonil** 22.5 g/L	**Metalaxyl-M** 14.4 g/L	**Sedaxane** 15.0 g/L
AOEL systemic	0.59 mg/kg bw/d	0.08 mg/kg bw/d	0.28 mg/kg bw/d
Inhalation absorption	100%	100%	100%

Oral absorption	100%	100%	100%
Dermal absorption	50% (default)	50% (default)	50% (default)

6.6.1 Selection of critical use and justification

The critical GAP used for the exposure assessment of the plant protection product is shown in Table 6.1-4. A list of all intended uses within the EU is given in Part B, Section 0.

Justification

A20607B is to be applied to sugar beet at a rate of 33.3 mL/seed unit. A seed unit is 100,000 seeds. It is expected that up to 1500 units of sugar beet will be treated per day.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

A summary of the exposure model used for estimation of operator exposure to the active substance during application of A20607B according to the critical use is presented in Table 6.6-2. The outcome of the estimation is presented in Table 6.6-3 (longer term exposure). Detailed calculations are in Appendix 3. At this time, no acute AOEL has been set for any of the active substances. Consequently, no acute risk assessment has been provided for these active substances.

Table 6.6-2: Exposure models for intended uses

Critical use	Sugar beet seeds (max. 99.9 L product/day)
Model	SeedTROPEX sugar beet treatment study data (75th percentile) [[redacted] (2006) Determination of operator exposure to imidacloprid during treatment of sugar beet seeds with IMPRIMO® in France. Amended Final Report 04B033 HI, Rhodia Recherches et Technologies, Laboratoire d'Hygiène Industrielle, F-69162 Saint-Fons Cedex, France. Unpublished. The data are property of the SeedTROPEX Group. (Syngenta File No. ASF654/0001)]

There are currently no representative data available in calculation models for the treatment of sugar beet seeds. In 2004 the Seed-TROPEX Group sponsored an operator exposure study on the treatment of sugar beet seeds in two treatment facilities in France. Exposure to fludioxonil, metalaxyl-M and sedaxane of operators treating small seeds with A20607B is calculated on the basis of this study.

Treatment of sugar beet seed takes place in closed systems (fluidized bed coaters, rotary drum coaters or granulators) and is a fully automatic process. Dosage of the chemicals is based on the amount of seed to be treated and a volume pumped per time unit; there is no manual calibration such as measuring a slurry volume. Sugar beet seed is normally packed into boxes of 1 unit each. Packing is fully automatic, with operator activities basically being limited to supplying the machine with stocks of packing material and to transporting pallets of packed seed to the storage room. Cleaning of equipment is partly automatic. Where manual cleaning is involved this is normally done by wiping or with pressurised water. The maximum treating capacity is estimated to be 1500 units/day.

The calculation of the estimated operator exposure is made with respect to the following personal protective equipment (PPE).

2004 Seed-	No PPE	Potential exposure (equivalent to no clothing)

TROPEX study (sugar beet)	PPE	Long work trousers, long-sleeved shirt and work jacket as usual work wear. <u>Protective clothing for mixing/loading:</u> Tyvek® coverall over outer dosimeter clothing, nitrile gloves, half-face mask at Mereville; Tyvek® coverall over outer dosimeter clothing, nitrile gloves, half-face mask, safety spectacles at Nerac. <u>Protective clothing for seed treatment, maintenance and cleaning:</u> Tyvek® coverall over outer dosimeter clothing, nitrile gloves, visor for drum washing with high-pressure water at Mereville; Tyvek® coverall over outer dosimeter clothing, disposable nitrile gloves, safety spectacles during cleaning at Nerac. The estimated actual dermal exposure values, therefore, reflect these levels of PPE.

Extrapolation of the Seed-TROPEX Study data is carried out as follows:

- Contamination due to dermal exposure is calculated on the basis of µg a.s / kg a.s. handled for activities related to seed treatment (mixing/loading and supervision/maintenance/cleaning of equipment).
- Extrapolation of inhalation exposure is done on the basis of µg a.s. / kg a.s. handled for activities related to seed treatment (mixing/loading and supervision/maintenance/cleaning of equipment).

Table 6.6-3: Estimated operator exposure

		Fludioxonil		**Metalaxyl-M**	
Model data	**Scenario**	**Total absorbed dose (µg/kg/day)**	**% of systemic AOEL**	**Total absorbed dose (µg/kg/day)**	**% of systemic AOEL**
Application rate		1.125 kg a.s./day		0.72 kg a.s./day	
Seed treatment (SeedTROPEX sugar beet model**;** 75th percentile) Body weight: 60 kg	Mixing/loading	0.0782	0.01	0.0501	0.06
	Supervision/maintenance/ cleaning equipment	0.633	0.11	0.405	0.51
	Combined	0.7112	0.12	0.455	0.57
Seed treatment (SeedTROPEX sugar beet model**;** 75th percentile) Body weight: 70 kg	Mixing/loading	0.067	0.01	0.0429	0.05
	Supervision/maintenance/ cleaning equipment	0.543	0.09	0.347	0.43
	Combined	0.61	0.10	0.39	0.49
		Sedaxane			
Model data	**Scenario**	**Total absorbed dose (µg/kg/day)**		**% of systemic AOEL**	
Application rate		0.75 kg a.s./day			
Seed treatment (SeedTROPEX sugar beet model**;**	Mixing/loading	0.0521		0.02	
	Supervision/maintenance/ cleaning equipment	0.422		0.15	

75th percentile) Body weight: 60 kg	Combined	0.4741	0.1693
Seed treatment (SeedTROPEX sugar beet model**;** 75th percentile) Body weight: 70 kg	Mixing/loading	0.0446	0.02
	Supervision/maintenance/ cleaning equipment	0.362	0.13
	Combined	0.410	0.15

Mobile treaters

The Seed-TROPEX model does not contain data for the assessment of exposure of operators treating seeds on mobile equipment.

For the following reasons exposure to operators treating seed on mobile equipment is considered to be in the same range or less than the exposure to operators working in static plants:

- Treatment on mobile equipment is usually done outside. This will most likely lead to lower levels of dust in the vicinity of the operators compared to working in a closed environment.
- Treatment capacities are estimated to be lower (0.5 to 2 tonnes/hour) on mobile equipment compared to static industrial equipment (estimated to be in the range of 2 to 9 tonnes/hour).
- Exposure time is likely to be shorter than in static plants because part of the working day is used for movement of the treatment equipment to the farms or between farms.

On-farm treatment

The Seed-TROPEX model does not contain data for the assessment of exposure of operators treating seeds using on-farm treatment equipment.

For the following reasons exposure to operators treating seed on-farm is considered to be in the same range or less than the exposure to operators working in static plants:

- Treatment on-farm is usually done outside. This will most likely lead to lower levels of dust in the vicinity of the operators compared to working in a closed environment.
- Treatment capacities are estimated to be lower (0.5 to 2 tonnes/hour) with on-farm equipment compared to static industrial equipment (estimated to be in the range of 2 to 9 tonnes/hour).
- Exposure time is likely to be shorter than in static plants because the operator will only treat sufficient seed for planting on the farm.

6.6.2.2 Measurement of operator exposure

Since there are no representative data available in calculation models, a field study measuring the operator exposure has been provided. A summary of the study is presented in 0.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY
HSE Chemicals Regulation Division (CRD), UK
Reviewer's comments: Toxicological endpoints to be used in the exposure assessment for 'Vibrance SB' The table below summaries the toxicological endpoints for metalaxyl-M to be used in the operator exposure risk assessment as agreed by the UK toxicological assessor for this Article 7 assessment.

Table 1. Summary of toxicological endpoints

	Metalaxyl-M
AOEL	0.08 mg/kg bw/day
Dermal absorption	Concentrate: 50%* Dilution: 50**

* Default value for FS formulation (EFSA Journal 2017; 15(6):4873)
**In-use dermal absorption value is not applicable as product is applied in concentrated form. Dermal absorption value for the concentrate has been used in instances where this value is required.

HSE notes that under this Article 7 evaluation of metalaxyl-M, the product 'Vibrance SB' (A20607B) has been evaluated as a representative use. Therefore, only non-dietary exposure to the active substance metalaxyl-M has been evaluated below. The product 'Vibrance SB' has not been considered fully nor is able to be authorised for use from the assessment below.

Operator Exposure

For the treatment of sugar beet seeds, the applicant has referenced the seed treatment study by [redacted] ([redacted], 2006 - "*Determination of operator exposure to imidacloprid during treatment of sugar beet seeds with IMPRIMO® in France."* Syngenta File No. ASF654/0001 / VV-379857). This study was evaluated by HSE for another product where Syngenta UK Limited is also the authorisation holder, therefore it is considered appropriate to use the data obtained in this study for the risk assessment of 'Vibrance SB'. A summary of the seed treatment study is presented below.

Summary of seed treatment study – [redacted]. (2006)

This study aimed to determine the dermal and inhalation exposure of operators exposed to imidacloprid during treatment of sugar beet seeds. The study was performed in two commercial seed treatment plants in France (Mereville and Nerac). The product is a water-based seed dressing liquid formulated as a flowable concentrate (FS) containing the insecticidal active substances imidacloprid and tefluthrin, however only exposure to imidacloprid was reported in the study.

Comparison of the test item 'Imprimo' in UK Seed treatment study with the proposed use of 'Vibrance SB'

	'Imprimo'	'Vibrance SB'
Formulation type	Flowable concentrate	Flowable concentrate
Active substance	Imidacloprid – 400 g/L Tefluthrin – 17.8 g/L	Metalaxyl-M – 14.4 g/L
Application rate of product (ml product /100,000 seed)	225 ml	33.3 ml
Application rate of active (g a.s./ 100,000 seeds)	90 g imidacloprid	0.48 g metalaxyl-M

The maximum application rate in the study was 90 g imidacloprid per 100,000 seed which is significantly higher than the proposed application rate of metalaxyl-M for this evaluation of 'Vibrance SB'. Therefore, this operator exposure study can be considered a worst case application rate for the evaluation of 'Vibrance SB'.

A total of 12 replicates were monitored (6 per site), with 4 replicates corresponding to mixing/loading (2 per site) and 8 replicates corresponding to the supervision, maintenance and cleaning activities (4 per site). The study report acknowledges that the number of replicates per task was lower than the requirement of 10 replicates per study in accordance with OECD guidance, based on a consideration of the size

of worker population involved in sugar beet seed treatment. Dermal and inhalation exposure was evaluated by using whole body dosimetry and personal air sampling.

Details of seed production process, seed treatment equipment, operator tasks, task durations and the PPE worn by operators were recorded in the study. Operators were monitored for tasks of mixing, loading, supervision, maintenance and cleaning. The seed treatment study did not measure operator exposure during the packing process. It is standard practice for sugar/fodder beet to be boxed using automatic packing systems with no operator handling of the seed. Therefore, the lack of exposure data during the packing process is considered acceptable.

Field recovery samples for the assessment of the stability of imidacloprid residues under field, transit and storage conditions on the dermal and inhalation exposure sampling matrices were performed at each field test site. The mean recoveries ranged between 77.0-105.8% at Mereville and 80.3-103.0% at Nerac. The study dosimetry results were corrected for where the average field recoveries for each matrix at each fortification level are less than 95%, in line with OECD guidance. The repeatability is within acceptable limits for all dosimeters at both sites (<20 % RSD).

Based on the residue measurements from the dosimeters, levels of actual dermal exposure (ADE) with the use of PPE in study and potential inhalation exposure (PIE) to imidacloprid were calculated. Potential inhalation exposure was calculated assuming a breathing volume of 20.83 litres/minute (default value in the EFSA guidance, expressed as 1.25 m^3/hr). PIE was also calculated with the use of FFP2 RPE assuming a 90% protection factor and FFP3 RPE assuming a 95% protection factor.

Estimate of operator exposure to metalaxyl-M during treatment of sugar and fodder beet seeds with 'Vibrance SB'

The product assessment used the results of the seed treatment study to estimate operator exposure. The study is more relevant for the risk assessment of operator exposure than the SeedTROPEX model as the study is specific to the treatment of sugar beet seeds, whereas the SeedTROPEX model does not contain data relevant to these processes.

The exposure estimate of operators to imidacloprid during the seed treatment study was converted to a rate in mg a.s./kg a.s. handled based on the amount of imidacloprid handled by the operators in the study. The exposure to metalaxyl-M during treatment with 'Vibrance SB' can then be estimated based on assumptions of the amount of metalaxyl-M operators will handle during treatment of sugar and fodder beet seeds. It has been assumed that 1500 units of seed will be treated with 'Vibrance SB' per day. This is considered a reasonable assumption, as between 482 and 1218 units of seeds were treated in the imidacloprid study. The proposed application rate of metalaxyl-M is 0.48 g a.s./unit of seeds, therefore it is assumed that operators will handle 0.720 kg a.s./day (rounded).

The imidacloprid seed treatment study did not measure operator exposure during the packing process. It is standard practice for sugar/fodder beet to be boxed using automatic packing systems with no operator handling of the seed therefore the lack of exposure data during the packing process is considered acceptable.

For operators carrying out cleaning activities, it was noted in the seed treatment study that operators would use a range of methods for cleaning equipment, including manual cleaning using sponge and water, removing equipment pieces to wash in sinks and using high pressure water to finish drum cleaning. Significant volumes of water were therefore used during the cleaning tasks at both sites.

In the seed treatment study during mixing and loading, operators may have been exposed to the diluted product. For example at Nerac, the 25 L product containers were rinsed with water, and the rinsing water was then transferred into the vessel used for mixture preparation. It is likely that the same practice was undertaken at Mereville as 25 L containers of product were also used. During the mixing/loading task at both sites high pressure water was used for cleaning. For example at Mereville, operators washed the

external part of the equipment with high-pressure water for approximately 5 minutes with an aerosol of water being observed and at Nerac, OP 12 washed the floor which had been contaminated with product with high pressure water.

The applicant's evaluation states that cleaning of seed treatment machinery is partially automated, and where manual cleaning is involved this is normally done by wiping or with pressurised water. In the seed treatment study during the cleaning task at both sites, significant volumes of water were used. At Mereville, operators needed to finish drum cleaning using high-pressure water and some parts of the equipment were removed and washed in a sink. At Nerac, several pieces of equipment were cleaned manually with water and a sponge. Some parts of the equipment were removed and washed in a sink. In the sink, high-pressure water was sometimes used for cleaning very dirty pieces (screws, injection nozzles etc.) for a few minutes. Several probes were also washed in the sink.

The operators undertaking the cleaning task are also likely to have been exposed to a wide range of much more diluted solutions when undertaking cleaning activities with water. Therefore, the measured imidacloprid residues on the dermal dosimeters will be to a range of dilutions during the cleaning task.

HSE has provided estimates of systemic exposure to metalaxyl-M during seed treatment with 'Vibrance SB' below. Estimates of exposure have been undertaken assuming 0.720 kg a.s. is handled per day and systemic exposure has been calculated using the individual body weight of the operators. As the concentration of metalaxyl-M in the concentrate is <5%, the agreed dermal absorption of metalaxyl-M in the concentrate is 50% based on the default value for FS formulations from Guidance on Dermal Absorption (EFSA Journal 2017; 15(6):4873). Since this is the default dermal absorption value for the dilution of FS formulations, this dermal absorption value of 50% is also assumed for the in-use dilution of 'Vibrance SB'. The dermal absorption value of 50% is therefore assumed in the assessment for all tasks.

Estimated systemic exposure to metalaxyl-M based on 0.720 kg a.s./day handled during seed treatment with 'Vibrance SB' using data from Mereville

Activity	Mixing/ Loading		Supervision/ Maintenance/Cleaning			
Operator number	OP2	OP5	OP1	OP3	OP4	OP6
ADE (mg/person)	0.012018	0.003015	0.021348	0.013188	0.012403	0.012054
PIE no RPE (mg/person)	0.000159	0.000088	0.002456	0.001178	0.000526	0.001780
PIE with FFP2 RPE (mg/person)	0.000016	0.000009	0.000246	0.000118	0.000053	0.000178
PIE with FFP3 RPE (mg/person)	0.000008	0.000004	0.000123	0.000059	0.000026	0.000089
Actual systemic exposure no RPE (mg/kg bw/day)	0.000073	0.000019	0.000239	0.000096	0.000122	0.000096
Actual systemic exposure with FFP2 RPE (mg/kg bw/day)	0.000072	0.000018	0.000199	0.000083	0.000114	0.000077
Actual systemic exposure with FFP3 RPE (mg/kg bw/day)	0.000072	0.000018	0.000196	0.000082	0.000113	0.000076
% AOEL no RPE	0.09	0.02	0.30	0.12	0.15	0.12
% AOEL with FFP2 RPE	0.09	0.02	0.25	0.10	0.14	0.10
% AOEL with FFP3 RPE	0.09	0.02	0.25	0.10	0.14	0.09

Estimated systemic exposure to metalaxyl-M based on 0.720 kg a.s./day handled during seed treatment with 'Vibrance SB' using data from Nerac

Activity	Mixing/ Loading		Supervision/ Maintenance/Cleaning			
Operator number	OP7	OP12	OP8	OP9	OP10	OP11

ADE (mg/person)	0.005419	0.014535	0.057280	0.034863	0.071770	0.101293
PIE no RPE (mg/person)	0.000087	0.000384	0.000265	0.000240	0.000155	0.000961
PIE with FFP2 RPE (mg/person)	0.000009	0.000038	0.000026	0.000024	0.000016	0.000096
PIE with FFP3 RPE (mg/person)	0.000004	0.000019	0.000013	0.000012	0.000008	0.000048
Actual systemic exposure no RPE (mg/kg bw/day)	0.000037	0.000094	0.000385	0.000209	0.000366	0.000637
Actual systemic exposure with FFP2 RPE (mg/kg bw/day)	0.000036	0.000090	0.000382	0.000207	0.000364	0.000626
Actual systemic exposure with FFP3 RPE (mg/kg bw/day)	0.000036	0.000090	0.000382	0.000206	0.000364	0.000626
% AOEL no RPE	0.05	0.12	0.48	0.26	0.46	0.80
% AOEL with FFP2 RPE	0.05	0.11	0.48	0.26	0.46	0.78
% AOEL with FFP3 RPE	0.05	0.11	0.48	0.26	0.46	0.78

Statistical estimates of the systemic exposure to metalaxyl-M (based on 0.720 kg a.s./day handled) during seed treatment with 'Vibrance SB' using data from both sites for the imidacloprid study is presented below. Statistical analysis has been conducted with data for the mixing/loading and supervision, maintenance and cleaning tasks separately and the data has then been combined to obtain an overall estimate of systemic exposure assuming an operator undertakes all tasks (similar to the exposure assessment presented in the core evaluation). Systemic exposure has been calculated assuming a 50% dermal absorption for all tasks.

Estimated systemic exposure to metalaxyl-M based on an assumed 50% dermal absorption value

	Combined systemic exposure during mixing/loading and supervision, maintenance and cleaning, no RPE		Combined systemic exposure during mixing/loading and supervision, maintenance and cleaning, FFP2 RPE		Combined systemic exposure during mixing/loading and supervision, maintenance and cleaning, FFP3 RPE	
	mg/kg bw/day	% AOEL	mg/kg bw/day	% AOEL	mg/kg bw/day	% AOEL
Empirical 75th percentile	0.000449	0.56	0.000445	0.56	0.000445	0.56
Parametric 75th percentile	**0.000457**	**0.57**	0.000441	0.55	0.000440	0.55
Empirical 95th percentile	0.000640	0.80	0.000628	0.79	0.000628	0.78
Parametric 9th percentile	0.001203	1.50	0.001239	1.55	0.001241	1.55
Maximum	0.000732	0.91	0.000717	0.90	0.000716	0.89

It is considered that for longer term exposure to operators, the estimate of systemic exposure should be the higher of the empirical or parametric 75th percentile. The estimated parametric 75th percentile, based on a 50% dermal absorption, is calculated to be 0.57% of the AOEL of metalaxyl-M with the use of PPE as specified in the study but without the use of RPE. This is within acceptable limits.

As discussed above, operators carrying out cleaning activities used significant volumes of water during the cleaning tasks at both sites, therefore the operators will have been exposed to a wide range of diluted solutions when undertaking cleaning activities with water. It is not possible to determine the range in dilutions that the operators were exposed to during cleaning. However, since the default dermal absorption value of 50% for the dilution of FS formulations has been used for the exposure assessment, it is considered that this value takes into account the uncertainty in the dermal absorption that the operators

were exposed to during cleaning with use of water.

The greatest level of ADE was reported for the supervision, maintenance and cleaning operators at Nerac. These operators used water to clean pieces of equipment in a sink, but they didn't use a high pressure water hose to clean the treatment drum. The operators at Nerac only wore coveralls during mixing and loading and cleaning activities.

During cleaning, operators at Mereville used a high pressure hose to clean the treatment drums which is likely to have caused an aerosol of water and product. This activity is likely to have led to the high PIE observed for the supervision, maintenance and cleaning operators at Mereville. However, the average dermal exposure for these operators is less than at Nerac, where cleaning the treatment drums with a high pressure water hose was not undertaken.

At Mereville, a 'Tyvek' coverall and protective gloves were worn during supervision, maintenance and cleaning activities and a face visor was also worn when the treatment drums were washed with high-pressure water. The use of this PPE seems to have mitigated dermal exposure to the supervision, maintenance and cleaning operators in Mereville in comparison to the operators at Nerac who didn't wear coveralls during the supervision and maintenance tasks and frequently handled treated seed and contaminated equipment with bare hands.

It is stated that 'Tyvek' coveralls were worn during cleaning activities, but it is not clear what the specific classification of these coveralls were according to BS EN 14605 Protective clothing against liquid chemicals. Given that high pressure hoses were used during cleaning it is considered precautionary that the use of EN 14605 Type 3 coveralls with liquid tight connections for the whole body, suitable protective gloves, and a visor should be worn during cleaning activities with water, to mitigate dermal exposure. Therefore the following operator protection phrase is required:

- Operators must wear suitable protective clothing (coveralls)*, suitable protective gloves and face protection (faceshield) when cleaning machinery.
  * With liquid tight connections for the whole body to at least EN 14605 Type 3 or equivalent.

Operators not directly involved in the seed-treatment process

The Seed-TROPEX model contains data which allows estimation of exposure of people working in the seed treatment plant, but who are not directly involved in the seed treatment process. The model contains exposure data for three forklift truck drivers operating in cereal seed treatment plants. Based on data for these forklift truck drivers, the geometric mean levels of potential dermal exposure and potential inhalation exposure were equivalent to 7.66×10^{-4} ml formulation/h and 8.74×10^{-6} ml formulation/h, respectively.

Assuming a duration of exposure of 8 hours, a bystander body weight of 60 kg and no protection provided by normal work wear, systemic exposure resulting from the proposed use of 'Vibrance SB' is calculated for metalaxyl-M as follows:

$$\text{Systemic Exposure} = \frac{(PDE \times C \times DA) + (PIE \times C)}{BW}$$

Where:

PDE = Potential dermal exposure (ml product/8 hour day)
PIE = Potential inhalation exposure (ml product/8 hour day)
C = Concentration of active substance in product (mg/ml)
DA = Percentage dermal absorption
BW = Bodyweight (60 kg)

$$= \frac{(0.000766 \text{ ml/h} \times 14.4 \text{ mg/ml} \times 8 \text{ h} \times 50\%) + (0.00000874 \text{ ml/h} \times 14.4 \text{ mg/ml} \times 8 \text{ h})}{60}$$

= 0.0008 mg/kg bw/day, equivalent to 1% of the AOEL of metalaxyl-M.

The systemic potential exposure to metalaxyl-M is calculated to be 0.0008 mg/kg bw/day which is equivalent to 1% of the AOEL. This is within acceptable limits.

Operator exposure in mobile treaters and during on-farm treatment

The applicant has presented a case proposing to use 'Vibrance SB' as a treatment for sugar and fodder beet seeds in mobile treaters and as an on-farm treatment. As the Seed-TROPEX model does not contain data for the assessment of operator exposure to operators treating seeds via mobile equipment, this is assessed on a case-by-case basis.

The applicant has proposed that the use of 'Vibrance SB' on sugar and fodder beet seeds is acceptable due to the following reasons.

Mobile plants:

- Treatment on mobile equipment is usually done outside. This will most likely lead to lower levels of dust in the vicinity of the operators compared to working in a closed environment.
- Treatment capacities are estimated to be lower (0.5 to 2 tonnes/hour) on mobile equipment compared to static industrial equipment (estimated to be in the range of 2 to 9 tonnes/hour).
- Exposure time is likely to be shorter than in static plants because part of the working day is used for movement of the treatment equipment to the farms or between farms.

On-farm treatment:

- Exposure to operators treating seed on-farm is considered to be in the same range or less than the exposure to operators working in static plants:
- Treatment on-farm is usually done outside. This will most likely lead to lower levels of dust in the vicinity of the operators compared to working in a closed environment.
- Treatment capacities are estimated to be lower (0.5 to 2 tonnes/hour) with on-farm equipment com-pared to static industrial equipment (estimated to be in the range of 2 to 9 tonnes/hour).
- Exposure time is likely to be shorter than in static plants because the operator will only treat sufficient seed for planting on the farm.

HSE agrees with the applicants case. The operator exposure assessment conducted above is considered to be a worst-case exposure estimate. HSE agrees that treatment in mobile plants or on-farm has a much lower treatment capacity and is usually performed outdoors, ensuring that exposure is within the risk envelope of what has been assessed above. Therefore, exposure to metalaxyl-M from the use of 'Vibrance SB' on sugar and fodder beet seeds in mobile plants and on-farm treatment is within the risk envelope of what is assessed above.

Operator Protection Phrases

'Vibrance SB' is classified with respect to human health. The classification and resulting PPE requirements are listed in the following table.

H Phrase	PPE
H351: Suspected of causing cancer	No PPE. Effect considered in setting of AOEL

Considering the classification of 'Vibrance SB' and the operator exposure risk assessment with seed treatment study, the following operator protection phrases would be required on the seed treatment product label (if the product underwent a full assessment):

- Operators must wear suitable protective clothing (coveralls) and suitable protective gloves when handling the concentrate, contaminated surfaces or handling treated seed.

- Operators must wear suitable protective clothing (coveralls)*, suitable protective gloves and face protection (faceshield) when cleaning machinery.
  * With liquid tight connections for the whole body to at least EN 14605 Type 3 or equivalent.

6.6.3 Worker exposure (KCP 7.2.3)

6.6.3.1 Estimation of worker exposure

Table 6.6-4 shows the exposure model used for estimation of worker exposure during the loading and sowing of seeds treated with A20607B according to the critical use. The outcome of the estimation is presented in Table 6.6-5 (longer term exposure). Detailed calculations are in Appendix 3. At this time, no acute AOEL has been set for any of the active substances. Consequently, no acute risk assessment has been provided for these active substances.

Table 6.6-4: Exposure models for intended uses

Critical use	Loading and sowing sugar beet seeds
Model	SeedTROPEX Maize sowing study data (75th percentile) [[redacted] (2007) Determination of operator exposure to imidacloprid during loading/sowing of GAUCHO® treated maize seeds under realistic field conditions in Germany and Italy. Amendment No 1 to Final Report. SGS Institut Fresenius, Im Maisel 14, D-65232 Taunusstein. Study No. IF-05/00328969; 25 October 2007. Unpublished. The data are property of the SeedTROPEX Group. (Syngenta file No. ASF654/0002)]

There are currently no representative data available in calculation models for the loading and sowing of sugar beet seeds using pneumatic precision sowing equipment. The SeedTROPEX Group sponsored a study in 2005 in Germany and Italy on loading and drilling maize seeds treated with imidacloprid. The purpose of the study was to obtain exposure data for operators using pneumatic precision sowing equipment. This type of equipment has become typical for mechanical seed sowing. Given the age of the seed sowing studies in the SeedTROPEX model and that these data were generated from the loading and sowing of cereal seeds, the maize sowing study is regarded to provide more appropriate data for estimating levels of exposure from loading and drilling sugar beet seeds than the 1993 SeedTROPEX studies.

The calculation of the estimated worker exposure is made with respect to the following personal protective equipment (PPE).

2005 Seed-	No PPE	Potential exposure (equivalent to no clothing)

TROPEX study (maize seed sowing)	PPE	Long work trousers, long-sleeved shirt and work jacket as usual work wear. Protective clothing for loading treated seeds: Chemical resistant gloves throughout the whole task Protective clothing for sowing treated seeds: Chemical resistant gloves when getting in direct contact with treated seeds or contaminated surfaces

The areas treated in the study ranged from 5.5 ha to 40.2 ha and the amount of active substance handled ranged from 0.64 to 3.5 kg a.s./day. If 40 ha were sown with A20607B, which would be a high work rate for sugar beet, the amount of fludioxonil, metalaxyl-M, and sedaxane handled per day would be 0.04 kg a.s./day, 0.025 kg a.s/day and 0.026 kg a.s./day respectively, which is significantly lower than the amounts of a.s. handled in the study. The exposure data are therefore normalised to reflect the much lower application rates of fludioxonil, metalaxyl-M and sedaxane.

Extrapolation of the Seed-TROPEX Study data to A20607B is carried out as follows:

- Contamination due to dermal exposure is calculated on the basis of mg a.s / kg a.s. handled for activities related to seed loading and sowing.
- Extrapolation of inhalation exposure is done on the basis of mg a.s. / kg a.s. handled for activities related to seed loading and sowing.

Table 6.6-5: Estimated worker exposure (longer term exposure)

		Fludioxonil		**Metalaxyl-M**	
Model data	**Level of PPE**	**Total absorbed dose (µg/kg bw/day)**	**% of systemic AOEL**	**Total absorbed dose (µg/kg bw/day)**	**% of systemic AOEL**
Application rate		0.019 kg a.s./day		0.012 kg a.s./day	
Seed sowing (SeedTROPEX maize sowing model**;** 75th percentile) Body weight: 60 kg	Gloves while loading hopper	0.2438	0.04	0.1558	0.19
Seed sowing (SeedTROPEX maize sowing model**;** 75th percentile) Body weight: 70 kg	Gloves while loading hopper	0.2090	0.04	0.1336	0.17
		Sedaxane			
Model data	**Level of PPE**	**Total absorbed dose (µg/kg bw/day)**		**% of systemic AOEL**	
Application rate		0.013 kg a.s./day			
Seed sowing (SeedTROPEX maize sowing model**;** 75th percentile) Body weight: 60 kg	Gloves while loading hopper	0.1634		0.06	
Seed sowing (SeedTROPEX maize	Gloves while loading hopper	0.1400		0.05	

sowing model; 75th percentile) Body weight: 70 kg			

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not applicable for seed treatment products.

6.6.3.3 Measurement of worker exposure

Since there are no representative data in available calculation models, a field study measuring the worker exposure has been provided. A summary of the study is presented in 0.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY

HSE Chemicals Regulation Division (CRD), UK

Reviewer's comments:

To assess exposure to workers loading and sowing treated sugar beet seeds, the applicant has referenced the worker exposure study from [redacted] (2008) "*Determination of operator exposure to imidacloprid during loading/sowing of GAUCHO® treated maize seeds under realistic field conditions in Germany and Italy."* Study No. IF-05/00328969. This study was evaluated by HSE for another product where Syngenta UK Limited is also the authorisation holder, therefore it is considered appropriate to use data from this study in the risk assessment of 'Vibrance SB'. The study is considered to provide representative surrogate data for loading and drilling sugar/fodder beet seeds using pneumatic precision sowing equipment. A summary of the worker exposure study is presented below.

Summary of worker exposure study – [redacted] (2008)

The worker exposure study was conducted on 16 sites in Italy and Germany during April and May 2005, to investigate the exposure of workers during loading and sowing maize seed treated with the product 'Gaucho' containing the active substance imidacloprid. The maize seeds were either treated 'Gaucho FS 600' in Germany or 'Gaucho FS 350' in Italy. At one site in Germany (worker OG) the seed loading rate of imidacloprid was much lower than the target rate, therefore exposure to this worker has not been considered further. The information below therefore is for 4 sites in Italy and 11 sites in Germany.

One worker was monitored at each site during loading of the seed hoppers and sowing of the maize seed. The farms selected used a range of different pneumatic sowing machines and many different local modes of maize sowing. The data of the study covered a broad range of sowing conditions and could be considered to be representative of maize sowing in Western Europe.

The areas for the sowing of maize ranged from 5.5 ha to 40.2 ha (average 14.3 ha) with a total working period between 5.1 – 8.2 hours (average 7 hours). Depending on local variation, the hoppers were filled 2 to 6 times and 1 to 3 different maize varieties were sown by each worker. The phases of seed loading lasted from 11 to 49 minutes with the seed sowing taking between 4.4 – 8.3 hours (average 6.7 hours).

Comparison of the test item with the proposed use of 'Vibrance SB'

Test item	'Vibrance SB'	'Gaucho FS 350' - Italy	'Gaucho FS 600'- Germany
Seeds	Sugar and fodder beet seeds	Maize seeds	Maize seeds

Active substance content of product	14.4 g/L metalaxyl-M	350 g/L imidacloprid	600 g/L imidacloprid
Seed loading	0.0048 mg a.s./seed	Target: 1.0 – 1.2 mg a.s./seed Actual: 1.0 – 1.2 mg a.s./seed (1.1 mg a.s./seed average)	Target: 1.0 mg a.s./seed Actual** 0.6 – 1.1 mg a.s./seed (0.9 mg a.s./seed average)
Sowing rate per hectare	130,000 seeds/ha	65,000 – 105,000 seeds/ha (85,000 seeds/ha average)	
A.s./ha	0.000624 kg a.s./ha	0.075 – 0.117 kg a.s./ha (0.095 kg a.s./ha average)	
Area sown in 1 day	20 ha*	5.5 – 40.15 ha (14.3 ha average)	

*The applicant has noted that a 40 ha work rate would be high for sowing sugar and fodder beet seeds. Therefore, the use of a more realistic area sown (20 ha) has been assessed for application of 'Vibrance SB'.
**The loading rate of seed used by operator OG was 0.02 mg a.s./seed, much lower than the target rate, therefore this operator has not been included in the estimation of exposure.

The target seed loading rate of 'Vibrance SB' is 0.0048 mg a.s./sugar/fodder beet seed which is lower than the actual seed loading rate of imidacloprid in the study of 0.6 – 1.2 mg a.s./ maize seed. The average amount of active substance applied per hectare in the study (0.095 kg a.s./ha) is higher than the proposed rate for 'Vibrance SB' of 0.000624 kg a.s./ha.

Given that the loading rate of a.s. on the seed in the study and the amount of active substance applied per hectare is greater in the study when compared to the proposed application rate of 'Vibrance SB' It is considered that the 'Gaucho' study can be used to estimate the systemic exposure to metalaxyl-M when loading and sowing 'Vibrance SB'.

Equipment

All sowing machines in this study were different variations of pneumatic precision seed drills which operated to the same basic principles. However, the design varied among the different manufacturers and models. The construction of the different sowing machines is likely to have some impact on abrasion of the coated material from the treated seed kernels. The abraded dust can pass through the holes of the seeding disc and can be blown through the outlet of the turbofan. At each site granular fertiliser was laid together with the maize seed into the furrow. Consequently additional hoppers were mounted to provide the fertiliser granules.

If the equipment had been used for sowing 'Gaucho' treated seed during the season before the monitoring, the corresponding sowing machine and the tractor cabin were cleaned by blowing out the empty hoppers with compressed air, wiping the lids with a moistened sponge and cleaning the wheel and the main handles inside the tractor cabin. The tractor cabin and the sowing machine were cleaned by the monitoring team. The hoppers were blown out by an independent person of the farm or in three cases by the future worker who took a shower before he dressed with the dosimeter clothing.

Worker Tasks

The main tasks of the workers were loading the hoppers of the sowing machines with treated maize seed and fertiliser and subsequent sowing of the seeds. A few of the workers also applied a herbicide to the soil (band spray application) during the sowing process.

Loading of the seed hoppers with 'Gaucho' treated maize seeds was always done manually. Typically, the worker tore or cut open the paper bag at one end, lifted it to the open top of the hopper and poured the seed into the hopper until it was completely filled. Very often the worker smoothed the top of the seed with gloved hands before he closed the lid of the hopper, even if gloves were not worn for the loading task. Worker OO was observed to smooth the top of the seed with bare hands.

Sowing procedures included sowing and other tasks such as loading of fertiliser and herbicide spray solutions as well as activities to maintain, adjust or repair the sowing machine and to check the level of remaining seed in the hoppers. During the fertiliser filling phase the worker was at a high risk of contamination because in most cases he had to climb on the sowing equipment. During the sowing phase the worker sat in a closed tractor cabin. The sowing phase could be interrupted if the worker had to check the appropriate distance of the seed in the furrow, check the settings of the machine or if he had to adjust or repair the equipment.

Dermal and Inhalation Exposure Sampling

Each worker was equipped with identical passive dosimeters comprising of long sleeved undershirt and long underpants, long shirt, long work trousers and work jacket. At the end of monitoring, the workers were undressed and the dosimeters collected for analysis. For the loading phase the workers were allowed to choose to wear protective nitrile gloves or to have bare hands. Workers were asked to wear gloves whenever they had to adjust, maintain or repair the sewing machine, which was considered as a part of the sowing phase. Filling the hoppers with fertiliser was considered to be part of the sowing phase. All workers wore protective gloves during loading of fertiliser. Actual dermal exposure to the hands was measured using a hand wash. Dermal exposure to the head and neck was sampled by performing face and neck wipes with pre-wetted cotton gauze pads.

To determine the potential inhalation exposure the workers were equipped with personal IOM samples, each consisting of a calibrated pump and filter cassette with the glass fibre filter (IOM filter). The sampling tube was fixed within the breathing zone of the worker. The inhalation exposure during the loading and sowing phases were monitored separately.

Field recovery samples for the assessment of the stability of imidacloprid residues during exposure time and shipping/storage conditions on the dermal and inhalation exposure sampling matrices were performed at eight out of the sixteen sites. The average recoveries ranged between 79-102%. Three samples showed low recovery values. As recovery levels generally showed repeatability with RSD of 10% or less, the argument that these three samples reflect some procedural error has been accepted. The study dosimetry results have been corrected for where the average field recoveries for each matrix at each fortification level are less than 95% in line with OECD guidance, with the suspected outliers excluded.

Based on the residue measurements from the dosimeters, levels of potential dermal exposure (PDE), actual dermal exposure (ADE) and potential inhalation exposure (PIE) to imidacloprid were calculated. Potential inhalation exposure was calculated assuming a breathing volume of 20.83 litres/minute (default value in the EFSA guidance, expressed as 1.25 m^3/hr).

Estimate of worker exposure to metalaxyl-M during treatment of sugar and fodder beet seeds with 'Vibrance SB'

The product assessment used the results of the seed treatment study to estimate worker exposure during loading and sowing of treated seeds. The study is more relevant for the risk assessment of worker exposure than the SeedTROPEX model as the study is specific to the loading and drilling of sugar/fodder beet seeds using pneumatic precision sowing equipment, whereas the SeedTROPEX model does not contain data relevant to these processes.

It is considered that contaminated dust is the main source of worker exposure during loading and sowing of treated seeds. The amount of active substance in the dust will depend on the treatment (loading) rate. In order for these study results for exposure to imidacloprid during loading and sowing maize seeds treated with 'Gaucho' to be used to estimate the exposure to metalaxyl-M during loading and sowing of 'Vibrance SB', the measured exposure values from the study have been normalised to the amount of substance handled (mg a.s./kg a.s. handled). This type of normalisation reflects the exposure in relation to the respective amount of active substance loaded to the seed.

An initial hand wash sample was undertaken at the start of the day to ensure there was no background contamination of imidacloprid to the hands. Even with the cleaning of the sowing equipment prior to the monitoring event, residues of imidacloprid were recorded in all of the initial hand wash samples before the start of monitoring. It is likely that the tractor/sowing equipment was contaminated with imidacloprid dust from previous seed sowing activities, and the workers may have come into contact with the contaminated equipment prior to monitoring. A small proportion of the contamination received by the workers during the monitoring of the loading and sowing of 'Gaucho' treated maize seed is therefore likely to come from contact with dust on the sowing equipment from previous seed sowing with imidacloprid treated seeds. This proportion of the exposure is not related to the amount of active substance loaded on the seeds during this sowing event, therefore the normalisation of this proportion of exposure in related to active substance handled is not relevant. However, since it is not possible to separate the contamination received from previous sowing events during the monitoring period it is considered appropriate to include the first hand wash sample in the data set and to normalise the full dosimeter results in relation to the amount of active substance handled during this sowing event.

HSE has provided estimates of systemic exposure to metalaxyl-M during loading and sowing of sugar/fodder seed treated with 'Vibrance SB', using the exposure data from the 'Gaucho' exposure study normalised to the amount of active substance handled.

The following assumptions have been made for the estimate of worker exposure to metalaxyl-M during the loading and sowing of 'Vibrance SB' treated sugar/fodder beet seeds:

Seed handled:	Sugar/fodder beet
Seed treatment (loading rate):	0.0048 mg metalaxyl-M/seed
Sowing rate per ha:	130,000 seeds
Amount of a.s. handled per ha:	0.624 g metalaxyl-M/ha
Area to be sown in one day:	20 ha
Amount of a.s. handled per day:	0.01248 kg metalaxyl-M/day
Dermal absorption:	50%*
Inhalation absorption:	100%
Worker body weight:	Individual worker body weights from the study
Worker clothing:	Long sleeved work wear. Protective gloves worn when in direct contact with treated seed or contaminated surfaces.

* Dermal absorption of the concentrate and dilution assumed to be 50% in line with the default value for FS formulation (EFSA Journal 2017; 15(6):4873).

Systemic exposure to metalaxyl-M during loading and sowing of 'Vibrance SB' treated sugar beet seeds has been calculated using the normalised exposure to imidacloprid from the 'Gaucho' exposure study using the following equation:

$$\text{Systemic exposure [mg/kg bw/day]} = \frac{(\text{ADE} \times \text{DA} + \text{PIE}) \times \text{AH}}{\text{BW}}$$

ADE = Actual dermal exposure during loading and sowing in mg a.s./kg a.s. applied.
PIE = Potential inhalation exposure during loading and sowing in mg a.s./kg a.s. applied assuming a breathing rate of 20.83 m^3/hr.
DA = Dermal absorption (50%)
BW = Body weight in kg
AH = Amount of metalaxyl-M handled during a day with a 20 ha/day work rate (0.01248 kg metalaxyl-M/day)

All the workers used closed cabin tractors during sowing of the treated maize seed, although it is not known whether any of the tractors had a certified dust filtration system. To estimate the exposure to

workers undertaking sowing without a closed cabin, the maximum residues reported on the IOM samplers mounted to either the left side or the right side of the tractor cabin have been added to the residues recorded on the workers personal IOM samplers. This combined PIE assumes a breathing rate of 20.83 m^3/hr.

The estimated total systemic exposure to metalaxyl-M during loading and sowing of 'Vibrance SB' treated sugar/fodder beet seed based on the normalised data from the 'Gaucho' study is given below.

Total systemic exposure to metalaxyl-M during loading and sowing of 'Vibrance SB' treated sugar/fodder beet seed

Worker	Actual Systemic Exposure to metalaxyl-M with closed cabin		Actual Systemic Exposure to metalaxyl-M with open cabin	
	mg/kg bw/day	% AOEL	mg/kg bw/day	% AOEL
OA	0.000089	0	0.000098	0
OB	0.000312	0	0.000333	0
OC	0.000535	1	0.000554	1
OE	0.000019	0	0.000023	0
OF	0.000018	0	0.000019	0
OH	0.000032	0	0.000036	0
OJ	0.000036	0	0.000050	0
OK	0.000091	0	0.000092	0
OL	0.000314	0	0.000329	0
OM	0.000082	0	0.000085	0
ON	0.000014	0	0.000017	0
OO	0.000068	0	0.000068	0
OP	0.000132	0	0.000166	0
OQ	0.000075	0	0.000086	0
OR	0.000182	0	0.000215	0
Empirical 75th percentile	0.00017	0.21	0.00020	0.25
Parametric 75th percentile	0.00021	0.26	0.00024	0.30

Systemic exposure has been calculated assuming the use of workwear and protective gloves when handling treated seeds or contaminated surfaces. Assuming 50% dermal absorption of metalaxyl-M and 100% absorption via inhalation.

For risk assessments in relation to longer term exposures, the EFSA Guidance notes that exposures should, as a default, be derived as the higher of:

(a) The 75th percentile of the distribution of measurements in the sample (the level of exposure an individual in the population can experience repeatedly each day over a season); or

(b) A statistical estimate of the 75th percentile for the theoretical population of measurements from which the sample was derived, under the assumption that this population has a log-normal distribution.

Based on the normalised results of the 'Gaucho' seed loading and sowing study the estimated exposure to metalaxyl-M during sowing and loading 'Vibrance SB' treated sugar/fodder beet seeds is 0.25% of the AOEL of metalaxyl-M with the use of an open cabin tractor and the use of protective gloves when handling treated seeds. This is within acceptable limits.

The following phrase should be included on the seed bag label:

- Operators must wear suitable protective gloves when handling treated seed and contaminated seed sowing equipment.

6.6.4 Resident and bystander exposure (KCP 7.2.2)

In industrial seed treatment facilities the incidental presence of bystanders can be excluded by technical management measures. If occurring, exposure of bystanders would be of short duration and normally lower than that of seed treatment operators who are occupationally exposed all day long. The same applies for seed loading and sowing activities. Therefore, it is reasonable to assume that there will be no undue risk to persons being incidentally exposed to seed treatment or seed sowing operations.

6.6.4.1 Estimation of resident and bystander exposure

Resident and bystander exposure not applicable for seed treatment products.

6.6.4.2 Measurement of resident and/or bystander exposure

Resident and bystander exposure not applicable for seed treatment products.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY
HSE Chemicals Regulation Division (CRD), UK
Reviewer's comments: The treatment of sugar and fodder beet seeds is usually performed in professional plants where access is restricted to people working at the plant. Therefore, it is considered that bystanders and residents will not be exposed to 'Vibrance SB' during the seed treatment process. Therefore, no resident/bystander exposure risk is expected. No further assessment is necessary.

6.6.5 Combined exposure

The product is a mixture of three active substances.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	<u>Toxicology:</u> Under the Article 7 evaluation of metalaxyl-M, the product Vibrance SB (A20607B) has been evaluated as a representative use. As such, only the toxicity of metalaxyl-M has been considered, therefore combined toxicity between active substances present in Vibrance SB (A20607B) has not been evaluated under the Article 7 evaluation.

6.6.5.1 Exposure assessment of metalaxyl-M, fludioxonil and sedaxane in A20607B

Note: The combined toxicological effect of these active substances has not been investigated with regard to repeated dose toxicity.

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-6: Risk assessment from combined exposure (long-term exposure)

Application scenario	Active ingredient	Estimated exposure / AAOEL (HQ)
Operators (60 kg) – treating seeds Gloves, coveralls, half-face mask and safety spectacles	Fludioxonil	0.0012
	Metalaxyl-M	0.0057
	Sedaxane	0.0017
	Cumulative risk operators (HI)	**0.0086**
Operators (70 kg) – treating seeds Gloves, coveralls, half-face mask and safety spectacles	Fludioxonil	0.0010
	Metalaxyl-M	0.0049
	Sedaxane	0.0015
	Cumulative risk operators (HI)	**0.0074**
Workers (60 kg) – sowing treated seeds Gloves when handling treated seed	Fludioxonil	0.0004
	Metalaxyl-M	0.0019
	Sedaxane	0.0006
	Cumulative risk workers (HI)	**0.0029**
Workers (70 kg) – sowing treated seeds Gloves when handling treated seed	Fludioxonil	0.0004
	Metalaxyl-M	0.0017
	Sedaxane	0.0005
	Cumulative risk workers (HI)	**0.0026**

The Hazard Index is < 1. Thus, combined exposure to all active substances in A20607B is not expected to present a risk for operators, workers, residents and bystanders. No further refinement of the assessment is required.

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY

HSE Chemicals Regulation Division (CRD), UK

Reviewer's comments:

Combined exposure

HSE notes that under the Article 7 evaluation of metalaxyl-M, the product 'Vibrance SB' (A20607B) has been evaluated as a representative use. Therefore, only non-dietary exposure to the active substance metalaxyl-M has been evaluated. Thus, a combined exposure assessment for the proposed uses of 'Vibrance SB' has not been considered.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP 7.1.1	[redacted]	20/03/2015	Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure) Report No. [redacted] Document No. VV-411770 , A20607B_10042 Test Facility [redacted] GLP Unpublished	Y	SYN
KCP 7.1.2	[redacted]	05/03/2015	Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) - Acute Dermal Toxicity Study in Rats Report No. [redacted] Document No. VV-411280 , A20607B_10029 Test Facility [redacted] GLP Unpublished	Y	SYN
KCP 7.1.3	[redacted]	30/03/2015	Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) – Acute Inhalation Toxicity Study (Nose-Only) in the Rat Report No. [redacted] Document No. VV-411785 , A20607B_10049 Test Facility [redacted] GLP Unpublished	Y	SYN
KCP 7.1.5	[redacted]	25/02/2015	Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) - Acute Eye Irritation Study in Rabbits Report No. [redacted] Document No. VV-411384 , A20607B_10032 Test Facility [redacted]	Y	SYN

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
			GLP Unpublished		
KCP 7.1.6	[redacted]	12/03/2015	Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) –Local Lymph Node Assay in the Mouse – Individual Method Report No. 41403291 Document No. VV-411911 , A20607B_10037 Test Facility [redacted] GLP Unpublished	Y	SYN
KCP 7.1.1	[redacted]	20/03/2015	Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure) Report No. [redacted] Document No. VV-411770 , A20607B_10042 Test Facility [redacted] GLP Unpublished	Y	SYN
KCP 7.2.1.1	[redacted]	2006	Determination of Operator Exposure to Imidacloprid during Treatment of Sugar Beet Seeds with IMPRIMO in France Syngenta Crop Protection AG, Basel, Switzerland RHODIA Recherches et Technologies, Lab d'Hygiene Industrielle, Saint-Fons, France, 04B033 HI GLP not published Syngenta File No. ASF654/0001 / VV-379857	N	Seed Tropex Group (SYN access)
KCP 7.2.3.1	[redacted]	2007	Determination of operator exposure to imidacloprid during loading/sowing of GAUCHO treated maize seeds under realistic field conditions in Germany and Italy Syngenta Crop Protection AG, Basel, Switzerland IF-05/00328969 GLP	N	Seed Tropex Group (SYN access)

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
			not published Syngenta File No ASF654/0002		
KCA2 5.4.2	[redacted]	15/09/2017	CGA226048 - Oral (Gavage) Mouse Micronucleus Test Report No. [redacted] Document No. VV-468462 , CGA226048_10000 Test Facility [redacted] GLP Unpublished	Y	SYN

List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner

List of data submitted by the applicant and not relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCA2 5.4.2	[redacted]	27/01/2015	Metalaxyl-M - Oral (Gavage) Mouse Micronucleus Test Report No. [redacted] Document No. VV-411540 , CGA329351_11683 Test Facility [redacted] GLP Unpublished	Y	SYN

List of data relied on not submitted by the applicant but necessary for evaluation

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

A 2.2 Acute oral toxicity (KCP 7.1.1)

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant proposes to meet the data requirement for acute oral toxicity using a study previously evaluated by HSE. The study was evaluated during the following zonal application. Based on the available study, HSE concluded that the acute oral LD_{50} was > 5000 mg/kg bw. Conclusion Based on the available study, the acute oral LD_{50} was > 5000 mg/kg bw, therefore the product does not meet the criteria for classification for acute oral toxicity in accordance with Regulation 1272/2008 (CLP).

Reference	KCP 7.1.1
Report	[redacted], 2015 Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) - Acute Oral Toxicity Study in the Rat (Up and Down Procedure). [redacted] A20607B_10042
Guideline(s)	Yes. Acute Oral Toxicity (rat): OECD Test Guideline 425 (2008): EPA OPPTS 870.1100 (2002)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A20607B / Vibrance SB (SMU4DP001)
Species	Rat, CRL(WI)

No. of animals (group size)	3 rats (female)
Dose(s)	5000 mg/kg bw
Exposure	Once by gavage
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of A20607B / Vibrance SB

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Female rats				
5000	0/3/3	24 hours	Day 14	> 5000

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 2: Summary of findings of acute oral toxicity study in rats of A20607B / Vibrance SB

Mortality	No mortality occurred.
Clinical signs	Clinical signs such as decreased activity, incoordination and hunched back position were noted in the first 24 hours post-treatment, all animals were symptom free afterwards.
Body weight	Body weight gain was considered to be normal.
Macroscopic examination	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the oral LD_{50} of A20607B / Vibrance SB is higher than 5000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.3 Acute percutaneous (dermal) toxicity (KCP 7.1.2)

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant proposes to meet the data requirement for acute dermal toxicity using a study previously evaluated by HSE. The study was evaluated during the following zonal application. Based on the available study, HSE concluded that the acute dermal LD_{50} was > 5000 mg/kg bw. Conclusion Based on the available study, the acute dermal LD_{50} was > 5000 mg/kg bw, therefore the

	product does not meet the criteria for classification for acute dermal toxicity in accordance with Regulation 1272/2008 (CLP).

Reference	KCP 7.1.2
Report	[redacted], 2015 Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) - Acute Dermal Toxicity Study in Rats. [redacted] A20607B_10029
Guideline(s)	Yes. Acute Dermal Toxicity (rat) OECD 402 (1987): OPPTS 870.1200 (1998); EC 440/2008 (2008)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A20607B / Vibrance SB (SMU4DP001)
Species	Rat, CRL: WI
No. of animals (group size)	10 rats (5 male & 5 female)
Dose(s)	5000 mg/kg bw
Exposure	24 hours (dermal, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 3: Results of acute dermal toxicity study in rats of A20607B / Vibrance SB

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Male rats				
5000	0/0/5	-	Day 14	> 5000
Female rats				
5000	0/0/5	-	Day 14	> 5000

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 4: Summary of findings of acute dermal toxicity study in rats of A20607B / Vibrance SB

Mortality	No mortality occurred.
Clinical signs	No clinical signs of toxicity were observed.

Body weight	Body weight gain was considered to be normal.
Macroscopic examination	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the dermal LD_{50} of A20607B / Vibrance SB is higher than 5000 mg/kg bw in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant proposes to meet the data requirement for acute inhalation toxicity using a study previously evaluated by HSE. The study was evaluated during the following zonal application. Based on the available study, HSE concluded that the acute inhalation LC_{50} was 6.1 mg/L. Conclusion Based on the available study, the acute inhalationl LC_{50} was 6.1 mg/L, therefore the does product not meet the criteria for classification for acute oral toxicity in accordance with Regulation 1272/2008 (CLP).

Reference	KCP 7.1.3
Report	[redacted], 2015 Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) Acute Inhalation Toxicity Study (Nose-Only) in the Rat. [redacted] A20607B_10049
Guideline(s)	Yes. Acute Inhalation Toxicity (rat): OECD 403 (2009); EPA OPPTS 870.1300 (1998); EC 440/2008, B.2 (2008)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A20607B / Vibrance SB (SMU4DP001)
Species	Rat, CRL: (WI) Wistar
No. of animals (group size)	10 rats (5 male & 5 female)

Concentration(s)	6.10 mg/L air
Exposure	4 hours (nose only)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 5: Concentration(s) and exposure conditions

Group	Nominal conc. (mg/L air)	Actual conc. (mg/L air)	MMAD * (µm)	GSD ** (µm)
0.1 (Sighting Exposure)	86.27	4.63	2.58	2.01
1 (Main Study)	100.29	6.10	3.38	1.83

* MMAD = Mass Median Aerodynamic Diameter
** GSD = Geometric Standard Deviation

Table A 6: Results of acute inhalation toxicity study in rats of A20607B / Vibrance SB

Concentration (mg/L air)	Toxicological results *	Duration of signs	Time of death	LC_{50} (mg/L air) (14 days)
Male rats				
6.10	0/1/5	Day 2	Day 14	>6.10
Female rats				
6.10	0/0/5	-	Day 14	>6.10

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 7: Summary of findings of acute inhalation toxicity study in rats of A20607B / Vibrance SB

Mortality	No mortality occurred.
Clinical signs	Slight laboured respiration and increased respiratory rate were noted in majority of the exposed animals on the day of exposure. No significant clinical signs were recorded in the exposed animals from the day following exposure until the end of the observation period, with the exception of one male from main group where sneezing was recorded on Day1-2.
Body weight	Normal bodyweight gain was noted for all exposed animals with the exception of few occasions where slight bodyweight loss was noted during the first three days of the observation period (three animals from the main group).
Macroscopic examination	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the inhalation LC_{50} of A20607B / Vibrance SB is higher than 6.10 mg/L air in rats. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.5 Skin irritation (KCP 7.1.4)

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant proposes to meet the data requirement for skin irritation using a study previously evaluated by HSE. The study was evaluated during the following zonal application. Based on the available study, HSE concluded that the mean erythema and oedema scores for 24-72 hours were 0. Conclusion Based on the available study, the criteria for classification in Category 2 for skin irritation were not met. Therefore, the product does not meet the criteria for classification for skin irritation in accordance with Regulation 1272/2008 (CLP).

Reference	KCP 7.1.4
Report	[redacted], 2015 Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) - Primary Skin Irritation Study in Rabbits. [redacted] A20607B_10015
Guideline(s)	Yes. Acute Skin Irritation (rabbit) OECD 404 (2002): OPPTS 870.2500 (1998); EC No 440/2008, B.4 (2008)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A20607B / Vibrance SB (SMU4DP001)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 (male)
Initial test using one animal	Yes
Exposure	0.5 mL (4 hours, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	3 days
Remarks	None

Results and discussions

Table A 8: Skin irritation of A20607B / Vibrance SB

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
00604	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	- -
00624	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	- -
00691	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	- -

* scores in the range of 0 to 4

Clinical signs:	No clinical signs of toxicity were observed.

Conclusion

Under the experimental conditions, A20607B / Vibrance SB is not a skin irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.6 Eye irritation (KCP 7.1.5)

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant proposes to meet the data requirement for eye irritation using a study previously evaluated by HSE. The study was evaluated during the following zonal application. Based on the available study, HSE concluded that the cornea opacity, iritis, conjunctive redness or oedema mean scores for 24-72 hours were 0. Conclusion Based on the available study, the criteria for classification in Category 2 for eye irritation were not met. Therefore, the product does not meet the criteria for classification for eye irritation in accordance with Regulation 1272/2008 (CLP).

Reference	KCP 7.1.5
Report	Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) - Acute Eye Irritation Study in Rabbits. [redacted], 2015 [redacted] A20607B_10032
Guideline(s)	Yes. Acute Eye Irritation (rabbit) OECD 405 (2012): EPA OPPTS 870.2400 (1998): EC No 440/2008, B.5 (2008): Directive 2004/73/EC B.5 (L 152 2004 29th April)

Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A20607B / Vibrance SB (SMU4DP001)
Species	Rabbit, New Zealand White
No. of animals (group size)	3 (Male)
Initial test using one animal	Yes
Exposure	0.1 mL (single instillation in conjunctival sac)
Irrigation (time point)	No
Vehicle/Dilution	None
Post exposure observation period	3 days
Remarks	None

Results and discussions

Table A 9: Eye irritation of A20607B / Vibrance SB

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
01440	Corneal opacity	1	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	2	0	0	0	0	-
	Chemosis conjunctivae	1	0	0	0	0	-
01437	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	2	0	0	0	0	-
	Chemosis conjunctivae	1	0	0	0	0	-
01442	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	-
	Redness conjunctivae	2	0	0	0	0	-
	Chemosis conjunctivae	1	0	0	0	0	-

* scores in the range of 0 to 4 for cornea opacity and chemosis, 0 to 3 for redness of conjunctivae and 0 to 2 for iritis

Clinical signs:	No clinical signs of toxicity were observed.

Conclusion

Under the experimental conditions, A20607B / Vibrance SB is a mild eye irritant. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant proposes to meet the data requirement for skin sensitisation using a study previously evaluated by HSE. The study evaluated during the following zonal application. Based on the available study, HSE concluded that stimulation indices were reactions were 0.85, 1.32 and 1.12 for 25%, 50% and 100% concentrations respectively. Conclusion Based on the available study, the criteria for classification for skin sensitisation were not met. Therefore, the product does not meet the criteria for classification for skin sensitisation in accordance with Regulation 1272/2008 (CLP).

Reference	KCP 7.1.6
Report	[redacted], 2015 Sedaxane/Fludioxonil/Metalaxyl-M FS (A20607B) Local Lymph Node Assay in the Mouse. 41403291 A20607B_10037
Guideline(s)	Yes. OECD Guidelines for Testing of Chemicals No. 429. Skin Sensitisation: Local Lymph Node Assay (adopted: 22 July 2010); Commission Regulation (EC) No 440/2008 of 30. May 2008, B.42. Skin Sensitisation: Local Lymph Node Assay (Official Journal L 142, 31/05/2008)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	A20607B (SMU4DP001)
Species	Mouse, CBA/Ca (CBA/CaOlaHsd)
No. of animals (group size)	Preliminary irritation group: 1 mouse Test substance group: 15 mouse, 5 per group Vehicle control group: 5 mice Positive control group: n/a
Range finding	Yes
Exposure (concentration(s), no. of applications)	Topical induction = 100%, 50%. 25%
Vehicle	For the test substance was 1% pluronic L92 in distilled water.
Pretreatment prior to topical application	No
Reliability check	None

Remarks	None

Results and discussions

Table A 10: Results of skin sensitisation study of product code/name

Concentration (% v/v) in 1% pluronic L92 in distilled water	Animal Number	dpm/ Animal	Mean dpm/Animal (Standard Deviation)	Stimulation Index [a]	Result
Vehicle	1-1	2025.05	2137.22 (±398.21)	na	na
	1-2	2081.45			
	1-3	2830.42			
	1-4	1882.59			
	1-5	1866.61			
25	2-1	1609.05	1810.37 (±321.76)	0.85	Negative
	2-2	1884.08			
	2-3	2342.81			
	2-4	1570.99			
	2-5	1644.94			
50	3-1	4424.51	2817.68 (±1106.91)	1.32	Negative
	3-2	3191.34			
	3-3	1499.84			
	3-4	2152.27			
	3-5	2820.46			
100	4-1	3167.49	2392.24 (±452.99)	1.12	Negative
	4-2	2195.66			
	4-3	1992.00			
	4-4	2353.18			
	4-5	2252.89			

N/A = not applicable

Clinical signs:	No clinical signs of toxicity were observed.

Conclusion

Under the experimental conditions, A20607B / Vibrance SB is not a skin sensitiser. Thus, no classification is required according to Regulation (EC) No. 1272/2008.

A 2.8 Supplementary studies for combinations of plant protection products (KCP 7.1.7)

Not required.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co-formulant

Information regarding material safety data sheets of the co-formulants can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.9.2 Available toxicological data for each co-formulant

Available toxicological data for each co-formulant can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.10 Studies on dermal absorption (KCP 7.3)

No studies have been performed.

A 2.11 Other/Special Studies

A 2.11.1 Metalaxyl-M – Oral (Gavage) Mouse Micronucleus Test

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant submitted an in vivo micronucleus assay in the mouse to demonstrate the clastogenic potential of metalaxyl-M. This study was concluded not to be required for HSE regulative decision on the clastogenic potential of metalaxyl-M impurity CGA226048. The study has therefore not been evaluated.

Report author	[redacted]
Report year	2015
Report title	Metalaxyl-M – Oral (Gavage) Mouse Micronucleus Test.
Report No	[redacted]
Guidelines followed in study	OECD 474 (1997). Guideline for the testing of chemicals: Mammalian erythrocyte micronucleus test.
Major deviations from test guideline	None
Guidance in force at time of submission of supplementary dossier	OECD 474 (2016). Guideline for the testing of chemicals: Mammalian erythrocyte micronucleus test.

Differences between old and current guideline	The 2016 version of OECD 474 details 3 acceptable dosing and sampling regimens; the 1997 details 2 acceptable dosing and sampling regimens; OECD 474 2016 specifies clear requirements for demonstration of laboratory proficiency and maintenance of historical control data. Precise acceptance and evaluation criteria are specified in the 2016 version and comparisons to historical control data are required for both control and treated cultures. The OECD 474 2016 guideline specifies 4000 PCE should be scored for micronuclei and a total of 500 erythrocytes assessed for determination of toxicity. In the 1997 version these numbers were 2000 PCE and 200 eythrocytes respectively.
Previous evaluation	Yes
GLP/Officially recognised testing facilities	Yes

Reference	KCA 5.4.2
Report	Metaladxyl-M – Oral (Gavage) Mouse Micronucleus Test. [redacted] [redacted], 2015 Report No.[redacted] Syngenta File No. CGA329351_11683 / VV-411540
Guideline(s)	OECD 474 (1997): OPPTS 870.5395 (1998): 2000/32/EC 440/2008 B.12 (2008)
Deviations	No
GLP	Yes
Acceptability	Yes

EXECUTIVE SUMMARY

Metalaxyl-M was tested to evaluate its potential to cause damage to chromosomes or cell division apparatus, or to cause cell cycle interference, leading to micronucleus formation in polychromatic erythrocytes in the bone marrow of young adult mice.

In all phases, the dosing of the vehicle and test item was by oral (gavage) administration twice, separated by approximately 24 hours, where appropriate.

In the dose sighting phase, groups of two male mice were given Metalaxyl-M as an emulsion in 0.5 % w/v carboxymethylcellulose with 0.1 % v/v Tween 80 at 300, 500 or 400 mg/kg/day, in order to determine the maximum tolerated dose (MTD).

In the range-finding phase, groups of up to three male and/or three female mice were given Metalaxyl-M at 400 mg/kg/day or 200 mg/kg/day, in order to confirm the MTD in both male and female mice.

The MTD was confirmed as 400 mg/kg/day in male mice and 200 mg/kg/day in female mice. As there was no substantial inter-sex differences in toxicity (a difference in MTD of three-fold or greater), the main study was conducted in males only, with the high dose selected as 400 mg/kg/day.

A proof of exposure phase was conducted to demonstrate that the bone marrow was exposed to the test item. This was demonstrated by analysis of test item in the whole blood of treated animals. The presence of Metalaxyl-M was confirmed by analysis of the study samples alongside samples of blank matrix and matrix spiked with the test item.

For the main study phase, three groups, each of six male mice were dosed with 100, 200 or 400 mg/kg/day Metalaxyl-M on two successive days, separated by approximately 24 hours (Groups 2 to 4). A group of six male mice (negative control - Group 1) was dosed with the vehicle alone and a positive control group (Group 5), also of six male mice, was given a single 4 mg/kg intraperitoneal dose of Mitomycin C (MMC).

Animals were humanely killed approximately 24 hours after the first dose (Group 5) or second dose (Groups 1 to 4). Bone marrow was harvested from each animal and smears prepared. The stained slides were coded, 2000 polychromatic erythrocytes (PCE) per animal were scored for the presence of micronuclei and the group frequencies were statistically analysed.

There were no relevant statistically significant increases in micronucleus frequency in male mice treated at any dose level of Metalaxyl-M, compared with the negative control group.

There was no evidence of a statistically significant reduction in the PCE/NCE ratio in male mice treated with Metalaxyl-M, indicating a lack of toxicity of Metalaxyl-M to the bone marrow. However, proof of exposure to the bone marrow was demonstrated in the range-finding phase of the study.

The animals dosed with MMC, the positive control item, had statistically significant increases in the number of micronucleated cells compared to the concurrent control group, which demonstrated that the test system was capable of detecting a known clastogen and that the scorers were capable of detecting micronuclei. There was no statistically significant decrease in the PCE/NCE ratio in the positive control group, indicating a lack of toxicity to the bone marrow.

In conclusion, it can be stated that there was no evidence of clastogenicity or aneugenicity following oral (gavage) administration of Metalaxyl-M up to the MTD of 400 mg/kg/day in male mice. Therefore, Metalaxyl-M is considered to be neither clastogenic nor aneugenic in this bone marrow micronucleus assay.

Materials and methods

Test Material:	Metalaxyl-M
Description:	Yellowish liquid
Lot/Batch number:	SMU4DL761
Purity:	97 %
Stability of test compound:	Retest date :31 May 2019

Control Materials:

Negative control (if not vehicle) :	N/A	**Final Volume:** N/A	**Route:** N/A
Vehicle:	0.5 % w/v carboxymethyl-cellulose with 0.1 % v/v Tween 80	**Final Volume:** 10 mL/kg	**Route:** oral
Positive control :	Mitomycin C	**Final Doses:** 4 mg/kg	**Route:** i.p

Test Animals:

Species	Mouse
Strain	CD-1
Age/weight at dosing	5 – 6 weeks (at start of experiment); Main study: mean weight 31 g, range 26-35 g
Source	[redacted]
Housing	Up to 3/cage
Acclimatisation period	11 days
Diet	Pelleted standard diet, *ad libitum*
Water	Tap water, *ad libitum*
Environmental conditions	Temperature: 19-21°C Humidity: 46-70% Photoperiod: 12 hours dark/12 hours light

Test compound administration:

	Dose Levels	Final Volume	Route
Dose-Sighting Phase:	300, 500, 400 mg/kg/day (males only)	10 mL/kg b.w.	oral
Range-Finding Phase:	400 mg/kg/day (males and females) 200 mg/kg/day (females only)	10 mL/kg b.w.	oral
Main Study:	100, 200, 400 mg/kg/day males only	10 mL/kg b.w	oral

Study Design and Methods:

Study initiation date: 15 May 2014 (study plan issued).

Experimental start date: 15 May 2014 (first animal arrival).

Experimental termination date: 30 July 2014 (last day of slide scoring).

Preliminary Toxicity Assay: A maximum tolerated dose (MTD) was determined, based on toxicity observed over a 24 hour observation period following oral (gavage) administration twice, separated by approximately 24 hours.

A proof of exposure phase was conducted to demonstrate that the bone marrow was exposed to the test item. This was demonstrated by analysis of test item in the whole blood of treated animals. Blood samples were obtained via the orbital sinus route from all animals in the range-finding phase at 1 hour and 4

hours post-second dose and at termination of each group. In each case, 0.1 mL samples were taken into tubes containing K_2EDTA. Metalaxyl-M was recovered from mouse blood:water [1:1 (v/v)] using an appropriate analytical procedure, and the processed samples analysed by LC-MS/MS to confirm exposure to the compound. The presence of Metalaxyl-M was confirmed by analysis of the study samples alongside samples of blank matrix and matrix spiked with the test item.

Table A 11: Micronucleus Test: Experimental Design

Group number	Number of animals	Dose level (mg/kg/day) Metalaxyl-M
1	6	Negative Control
2	6	100
3	6	200
4	6	400
5	6	Positive Control MMC 4 mg/kg

Animals in Groups 1 to 4 were dosed twice, approximately 24 hours apart, with vehicle alone (negative control) or Metalaxyl-M. Group 5 animals (positive control) were given a single 4 mg/kg dose of MMC at a dose volume of 5 mL/kg.

Slide Preparation: The range-finder animals were not allowed to recover from the anaesthetic after the terminal blood sample approximately 24 hours after the second test item administration and death was confirmed by cervical dislocation. The main study animals in Groups 1 to 4 were humanely killed approximately 24 hours after the second test item and vehicle administration. Group 5 animals were humanely killed approximately 24 hours after the single administration of the positive control. The animals were killed by exposure to rising concentrations of carbon dioxide and death was confirmed by cervical dislocation. The femurs from all animals were exposed by dissection of the surrounding muscle and connective tissues, and the shank of the bones removed. The bone marrow cells from both femurs of each animal were aspirated into labelled centrifuge tubes using a syringe containing foetal bovine serum. The bone marrow cells were centrifuged, the supernatant withdrawn, and the cells re-suspended in a minimal volume of foetal bovine serum. One drop of cell suspension was placed on each of two slides and spread by drawing an edge of a clean glass microscope slide along from the drop to the end of the slide. All slides were left to air dry and age overnight before fixing for 5 minutes in methanol. Fixed slides were stained for 20 to 30 minutes in 11.5 % (v/v) Giemsa in Sorensen's buffer pH 6.8.

Slide Analysis: A unique, unambiguous code was devised for each animal, including the positive controls. Adhesive labels that covered the animal and group identity were affixed to each slide so that the analyst could see only the study number and the new code.

2000 polychromatic erythrocytes (PCE), including micronucleated PCE (MN-PCE), were counted for each animal. The numbers of normochromatic (NCE) and micronucleated NCE (MN-NCE) erythrocytes were also recorded for the first 1000 cells scored. Only areas of slides of good technical quality and appropriate staining characteristics were scored.

Results and discussions

Dose-sighting phase: There were no clinical signs observed following administration of Metalaxyl-M at 300 mg/kg/day. Clinical signs observed following administration at 500 mg/kg/day included decreased activity, slow breathing, piloerection, partially closed eyes, cold to touch, intermittent tremors and prostration. Animals were killed due to clinical condition two hours post first-dose. At 400 mg/kg/day, signs included decreased activity, slow breathing, partially closed eyes and unsteady gait. No significant body weight loss was observed.

Range-finding phase: Clinical signs observed in males following administration at 400 mg/kg/day included decreased activity, unsteady gait, slow breathing, eyes closed or partially closed and intermittent twitching. At 400 mg/kg/day in females, signs included decreased activity, unsteady gait, slow breathing,

eyes partially closed, intermittent twitching, prostration and loss of blink and righting reflex. Females were killed due to clinical condition one hour post first-dose. Administration to females at 200 mg/kg/day resulted in decreased activity, unsteady and abnormal gait, eyes partially closed and hunched posture.

Based on the results of this phase, the MTD was considered to be 400 mg/kg/day in males and 200 mg/kg/day in females. As the difference between the MTD in males and females was less than three-fold, the main study was conducted in male mice only.

There was no need to assess toxicity to the bone marrow and bone marrow smears were not analysed in the range-finding phase, as the presence of Metalaxyl-M was confirmed since the study sample chromatograms showed substantial Metalaxyl-M content when compared with those of blank matrix and matrix fortified with Metalaxyl-M.

Micronucleus test: There were no adverse clinical observations following administration of Metalaxyl-M to male mice at 100 mg/kg/day (Group 2). Nor were there any adverse clinical observations in Group 1 (negative control) or Group 5 (positive control). Decreased activity was observed in males following administration at 200 mg/kg/day (Group 3). Clinical signs observed in males following administration at 400 mg/kg/day (Group 4) included decreased activity, unsteady gait, slow breathing, eyes partially closed and intermittent tremors.

There were no statistically significant increases in micronucleus frequency in male mice treated at any dose level of Metalaxyl-M, compared with the negative control group.

There was no evidence of a statistically significant reduction in the PCE/NCE ratio in male mice treated with Metalaxyl-M, indicating a lack of toxicity of Metalaxyl-M to the bone marrow. However, proof of exposure to the bone marrow was demonstrated in the range-finding phase of this study.

The animals dosed with MMC, the positive control item, had statistically significant increases in the number of micronucleated cells compared to the concurrent control group, which demonstrated that the test system was capable of detecting a known clastogen and that the scorers were capable of detecting micronuclei. There was no statistically significant decrease in the PCE/NCE ratio in the positive control group, indicating a lack of toxicity to the bone marrow.

Conclusion

There was no evidence of clastogenicity or aneugenicity following oral (gavage) administration of Metalaxyl-M up to the MTD of 400 mg/kg/day in male mice. Therefore, Metalaxyl-M is considered to be neither clastogenic nor aneugenic in this bone marrow micronucleus assay.

Micronucleus Data: Negative Control vs. Treated Groups – Males

	Negative Control 0 mg/kg/day	Metalaxyl-M 100 mg/kg/day	Metalaxyl-M 200 mg/kg/day	Metalaxyl-M 400 mg/kg/day	MMC 4 mg/kg
N	6	6	6	6	6
Mean MN-PCE	1.50	0.83	0.83	1.00	64.50[WW]
SD	1.05	0.75	0.98	0.89	16.72
Mean MN-PCE +SD	2.55	1.59	1.82	1.89	81.22
Mean MN-PCE – SD	0.45	0.08	-0.15	0.11	47.78
Mean PCE/NCE ratio	0.57	0.63	0.61	0.70	0.41
SD	0.13	0.16	0.09	0.18	0.15

Mean PCE/NCE +SD	0.70	0.79	0.70	0.88	0.57
Mean PCE/NCE - SD	0.44	0.47	0.52	0.52	0.26

MMC: Mitomycin C
N: number of animals
WW: statistically significant (Wilcoxon's test) p<0.01
Note: any discrepancy in this table is due to rounding differences

Mouse Historical Control Data

Males Negative Control							
	N	Mean	SD	Range (mean +/- SD)		Range (min / max)	
PCE	249	2020.8	140.6	1880.2	2161.4	2000	3004
NCE/1000 cells	249	540.5	81.7	458.9	622.2	327	825
MN-PCE	249	1.5	1.5	-0.1	3.0	0	8
MN-NCE	249	0.3	0.6	-0.3	0.9	0	3
PCE/NCE Ratio	249	0.9	0.3	0.6	1.2	0.2	2.1
Males Positive Control							
	N	Mean	SD	Range (mean +/- SD)		Range (min / max)	
PCE	212	2024.5	152.5	1872.1	2177.0	2000	3010
NCE/1000 cells	212	640.6	94.8	545.8	735.4	372	918
MN-PCE	212	110.2	58.6	51.6	168.8	9	354
MN-NCE	212	0.7	0.9	-0.2	1.6	0	6
PCE/NCE Ratio	212	0.6	0.3	0.3	0.9	0.1	1.7

([redacted] 2014)

Assessment and conclusion by applicant

Assessment:

The study was performed according to the 1997 version of OECD 474 and was compliant with the guideline that was in force at that time. However there are minor deficiencies in the study when it is compared to the current version of OECD 474 (2016). Only 2000 polychromatic erythrocytes (PCE) per dose level and control were analysed for micronuclei and different assay acceptance and evaluation criteria used compared to those recommended by OECD 474 (2016). The historical control data were not described according to the requirements of OECD 474 (2016). Overall, all the differences are considered to have not impacted the integrity or validity of the data generated. The study is scientifically valid.

The test is considered to meet the acceptance criteria as defined by OECD 474 (2016):

- OECD 474 2016 specifies clear requirements for demonstration of laboratory proficiency and maintenance of historical control data. For the current study the performing laboratory has a well-established record in performing the assay.
- HCD should be expressed as 95% (control limit, control interval), previously whole range. In the study report ranges and mean +/- SD are presented. This has no impact on the current study.
- OECD 474 2016 Data acceptance and evaluation criteria are specified and comparisons to historical control data are required for both control and treated cultures. For the current study the negative control response was close to the mean value of the negative control HCD, and the positive

control response was similar to the mean positive control HCD response, additionally the positive control response was statistically significant. Hence, the study is fully acceptable.

- The concurrent vehicle control data are acceptable for addition to a historical control database.
- The concurrent positive controls induced a clear increase in micronucleated PCE compared with the concurrent vehicle control.
- OECD 474 2016: Requirement for proof of exposure of target tissue. In the current study bioanalytical data (qualitative determination in blood) are presented. These show the test substance to be systemically bioavailable.
- OECD 474 2016: 4000 PCE should be scored per animal in 5 animals for micronuclei and a 500 erythrocytes per animal assessed for determination of toxicity. In the 1997 version this was 2000 and 200 respectively. The test item was administered up to the MTD above which dose limiting toxicity was observed and systemic exposure was demonstrated by bioanalysis. In the current study 6 animals per treatment group were assessed for micronucleus formation in 2000 PCE per animal, in excess of the 1997 TG requirement. The Positive control gave a clear positive response, hence the sensitivity of the assay is demonstrated. An appropriate number of doses and cells has been analysed. Although <4000 PCE were examined per animal the data are consistently negative at 3 different dose levels. The reduced number of PCE examined per animals is considered to not have affected the sensitivity of the assay, additionally more animals per treatment group were used (six) than specified in the OECD TG (five).
- The criteria for the selection of highest dose are consistent with those described by OECD 474.
- OECD 474 2016: Test for statistical significance should be performed. Statistical analysis of the data was performed.
- OECD 474 2016: Trend test should be performed. A trend test was not performed on the data, however all treated groups had lower mean MN frequencies than the negative control group therefore a trend test would not provide any additional value to data interpretation.
- OECD 474 2016: Definition of “clear negative“ and “clear positive“ results. In the current study no increases in MN frequency were observed in treated groups, hence the criteria for study interpretation used in the report are satisfactory. Although no trend test was conducted the study may still be considered to be clearly negative.

Conclusion: The study complies with the data requirements given in Commission Regulation No 283/2013. The test substance does not induce micronuclei in the bone marrow of orally treated mice.

A 2.11.2 CGA226048 - Oral (Gavage) Mouse Micronucleus Test

EVALUATION, SUMMARY AND CONCLUSION BY REGULATORY AUTHORITY	
Name of authority	**HSE Chemicals Regulation Division (CRD), UK**
Reviewer's comments	Toxicology: The applicant submitted an in vivo micronucleus assay in the mouse to demonstrate the clastogenic potential of the metalaxyl-M impurity CGA226048 ([redacted] 2017). Evaluation The study " CGA226048- Oral (Gavage) Mouse Micronucleus Test ", was in compliance with Good Laboratory Practice (GLP) and followed OECD TG 474 (1997 version). There were no deviations from the test guideline and the study is acceptable. A range finding study consisting of 3 male and 3 female mice established the maximum tolerated dose at 2000 mg/kg bw/d, proof of bone marrow exposure was also confirmed. The doses for the main study were spaced by a factor of 2 resulting in doses of 0, 500, 1000, and 2000 mg/kg bw/d. Groups of six male mice were administered a dose twice oraly, spaced 24 hours apart, with a control group receiving the vehicle (0.5% HMPC) and a positive control group administered 1 mg/kg bw mitomycin C. Animals were sacrificed 24 hours post the final dose and bone marrow samples were collected and scored via stained slides. 2000 polychromatic erythrocytes (PCE), including micronucleated PCE (MN-PCE), were counted for each animal. The numbers of normochromatic erythrocytes (NCE) and micronucleated NCE (MN-NCE) were also recorded for the first 1000 cells scored. Results There were no statistically significant increases in micronucleus frequency in male mice treated at any dose level of CGA226048, compared with the negative control group. The frequencies of micronucleated PCEs for all test groups fell within the range of the historical control data for the negative control. Therefore, in accordance with the OECD test guideline, the criteria for a positive result have not been met. Conclusion During an GLP and OECD compliant study under the described experimental conditions reported, the test item did not induce micronuclei up to the maximum tolerated dose as determined by the micronucleus test in the bone marrow cells of the mouse. Therefore, CGA226048 considered to be non-genotoxic in this bone marrow micronucleus assay.

Report author	[redacted]
Report year	2017
Report title	CGA226048 - Oral (Gavage) Mouse Micronucleus Test
Report No	[redacted]

Guidelines followed in study	OECD 474 (2016). Guideline for the testing of chemicals: Mammalian erythrocyte micronucleus test.
Major deviations from test guideline	None
Guidance in force at time of submission of supplementary dossier	OECD 474 (2016). Guideline for the testing of chemicals: Mammalian erythrocyte micronucleus test.
Differences between old and current guideline	None
Previous evaluation	Yes
GLP/Officially recognised testing facilities	Yes

Reference	KCA 5.4.2
Report	CGA226048 - Oral (Gavage) Mouse Micronucleus Test. [redacted] (2017) Report No. [redacted], Syngenta File No. CGA226048_10000 / VV-468462
Guideline(s)	OECD 474 (2016): OPPTS 870.5395 (1998): 2000/32/EC 440/2008 B.12 (2008)
Deviations	No
GLP	Yes
Acceptability	Yes

EXECUTIVE SUMMARY

CGA226048 was tested to evaluate its potential to cause damage to chromosomes or cell division apparatus, or to cause cell cycle interference, leading to micronucleus (MN) formation in developing reticulocytes (RET) in the bone marrow of young adult mice.

In all phases, the dosing of the vehicle and test item was by oral (gavage) administration twice, approximately 24 hours apart.

In the range-finding phase, a group of 3 male and 3 female mice were given CGA226048 as a suspension in the vehicle, 0.5% hydroxypropylmethylcellulose (4000 cps) (HPMC) at 2000 mg/kg/day in order to determine the maximum tolerated dose (MTD) in both male and female mice. The MTD was confirmed as exceeding the guideline regulatory maximum dose level of 2000 mg/kg/day in male and female mice. As there was no inter-sex difference in toxicity, the main study was conducted in males only, with the high dose selected as 2000 mg/kg/day.

Proof of exposure was conducted as part of the range-finding phase to demonstrate that the bone marrow was exposed to the test item, via LC-MS/MS analysis of CGA226048 in the whole blood and plasma from animals taken at 15 minutes, 1, 4 and 24 hours after the second dose. The presence of CGA226048 was confirmed by analysis of the study samples using a validated method.

For the main study phase, 4 groups, each of 6 male mice were dosed with vehicle alone (negative Control) or 500, 1000 or 2000 mg/kg/day CGA226048 on 2 successive days, approximately 24 hours apart. A positive Control group, also of 6 male mice, was given a single 1 mg/kg intraperitoneal injection of Mitomycin C (MMC).

Blood samples were taken from all main study animals approximately 48 hours after the final dose administration. A minimum of 4000 and a maximum of approximately 20000 reticulocytes were scored for the presence of micronuclei for each animal and the frequency of micronucleated reticulocytes (MN-RET) was statistically analysed.

There were no statistically significant increases in MN-RET frequency in male mice given any dose level of CGA226048, compared with the negative Control group.

There were no relevant reductions in the percentage of reticulocytes (% RET) in mice given CGA226048 and, since proof of exposure to the blood and, hence, bone marrow was demonstrated in the range finding phase of the study, this indicated a lack of toxicity of CGA226048 to the bone marrow.

The animals dosed with MMC, the positive Control item, had statistically significant increases in the number of MN-RET compared with the concurrent Control group which demonstrated that the test system was capable of detecting a known clastogen. There was a statistically significant decrease in the % RET in the positive Control group, indicating toxicity to the bone marrow. Animal 29 showed no increase in the number of MN-RET detected and no decrease in the % RET, indicating that there was no apparent effect of the positive Control. It was considered that this animal had been dosed incorrectly and the data from this animal were not included in the statistical analysis.

In conclusion, it can be stated that there was no evidence of clastogenicity or aneugenicity following oral (gavage) administration of CGA226048 up to 2000 mg/kg/day in male mice. CGA226048 is considered to be neither clastogenic nor aneugenic in the mouse micronucleus test.

Materials and methods

Test Material:	CGA226048
Description:	White to off-white crystalline powder
Lot/Batch number:	BPS 659/2
Active Ingredient Content (CGA226048)	99.0 % (± 2 %) (w/w)
Stability of test compound:	Retest date: 30 September 2018

Control Materials:

Negative control (if not vehicle) :	N/A	**Final Volume:** N/A	**Route:** N/A
Vehicle:	0.5 % hydroxypropylmethylcellulose (4000 cps)	**Final Volume:** 10 mL/kg	**Route:** oral
Positive control :	Mitomycin C	**Final Doses:** 1 mg/kg	**Route:** i.p.

Test Animals:

Species	Mice
Strain	Crl:CD-1
Age/weight at dosing	6 – 7 weeks (at start of experiment); Main study: range 29 g to 37 g mean weight 34 g
Source	[redacted]
Housing	3/cage
Acclimatisation period	11 days
Diet	Pelleted standard diet, *ad libitum*
Water	Tap water, *ad libitum*
Environmental conditions	Temperature: 19-21 °C Humidity: 48 % to 55 % Photoperiod: 12 hours dark/12 hours light

Test compound administration:

	Dose Levels	Final Volume	Route
Preliminary:	Range-finding phase: 2000 mg/kg/day (males and females)	10 mL/kg b.w.	oral
Main Study:	500, 1000, 2000 mg/kg/day males only	10 mL/kg b.w.	oral

Study Design and Methods:

Study initiation date: 20 March 2017 (study plan issued).

Experimental start date: 30 March 2017 (first animal arrival).

Experimental termination date: 12 July 2017 (last day of analysis).

Preliminary Toxicity Assay: Dosing was by oral (gavage) administration twice, separated by approximately 24 hours. Animals were observed periodically for up to 48 hours after the second dose.

Since bone marrow is well perfused, exposure of the bone marrow to the test item was assessed indirectly by collection of blood and plasma and analysis for CGA226048. Blood samples were obtained via the lateral tail vein from all animals in the range-finding phase at 15 minutes, 1, 4 and 24 hours after the second dose. At each collection, 100 µL samples were taken into tubes containing K_2EDTA anticoagulant and gently flicked to mix. Immediately following collection of each sample, 25 µL of whole blood was accurately measured into a polypropylene tube containing exactly 75 µL of acidified acetonitrile (1 % v/v formic acid in acetonitrile) [(1:3 (v/v)], vortexed and placed directly onto dry ice. Residual blood was placed on a roller to mix and then held in ice until centrifuged (3000 g, 5 minutes, at approximately 4 °C). 25 µL of the resultant plasma was aliquoted into tubes containing exactly 75 µL of acidified acetonitrile within 30 minutes of sampling. All samples were stored frozen (≤ -70 °C), before analysis. Concentrations of CGA226048 were determined using a validated bioanalytical method.

Table A 12 Micronucleus Test: Experimental Design

Group number	Number of animals	Dose level (mg/kg/day) CGA226048
1	6	Negative Control
2	6	500
3	6	1000
4	6	2000
5	6	Positive Control MMC 1 mg/kg

Animals in Groups 1 to 4 were dosed twice, approximately 24 hours apart, with vehicle alone (negative Control) or CGA226048 at a dose volume of 10 mL/kg. Group 5 animals (positive Control) were given a single 1 mg/kg dose of MMC at a dose volume of 5 mL/kg.

Animals were observed periodically for 48 hours after the last dose.

Slide Preparation: Range-finder animals were killed after the terminal blood sampling, approximately 48 hours after the second administration of the test item. The bone marrow cells from the femurs were aspirated into an individually labelled centrifuge tube containing foetal bovine serum and centrifuged. The supernatant was withdrawn and the cells were re-suspended in a minimal volume of foetal bovine serum. One drop of cell suspension was placed on each of two slides and spread. All slides were left to air dry and age overnight before fixing for five minutes in methanol. Fixed slides were stained for 20 to 30 minutes in 11.5 % (v/v) Giemsa in Sorensen's buffer pH 6.8.

Processing of blood samples for micronucleus evaluation: The main study animals in Groups 1 to 4 were killed approximately 48 hours after the second test item or vehicle administration. Group 5 animals were killed approximately 48 hours after the single administration of the positive Control. A terminal blood sample was taken for micronucleus scoring into tubes containing K_2EDTA anticoagulant and the animals were then killed by a Schedule 1 method. Blood samples were diluted in anticoagulant/diluent, supplied by Litron Laboratories, prior to fixation. Blood samples were then fixed in two separate methanol aliquots and stored at ≤ -70 °C for at least 3 days. One set of samples was then washed out of fixative and analysed. The remaining set of samples was transferred to long term storage solution for continued storage at ≤ -70 °C.

Scoring of micronuclei: All samples from the main study, along with quality control samples, were analysed by the same assay programme on a FACSVerse flow cytometer. A minimum of 4000 and a maximum of approximately 20000 RET were scored for the presence of MN for each animal.

Results and discussions

Preliminary toxicity assay: There were no adverse clinical observations and no effects on body weight following administration of CGA226048 at 2000 mg/kg/day.

Based on the results of this phase, the MTD was considered to exceed the guideline regulatory maximum dose level of 2000 mg/kg/day in males and females. As there was no difference in toxicity between males and females, the main study was conducted in male mice only.

Exposure to CGA226048 was confirmed by the presence of CGA226048 in range-finder blood and plasma samples taken 15 minutes, 1 and 4 hours after the second dose. Bone marrow smears were not analysed in the range-finding phase since the presence of CGA226048 was confirmed in the blood and plasma samples.

Micronucleus test: There were no adverse clinical observations following administration of CGA226048 to male mice at any dose level. Nor were there any adverse clinical observations in Group 1 (negative Control) or Group 5 (positive Control).

There were no statistically significant increases in MN-RET frequency in male mice given any dose level of CGA226048, compared with the negative Control group.

There was no evidence of a statistically significant reduction in the % RET in male mice given CGA226048, indicating a lack of toxicity of CGA226048 to the bone marrow. However, proof of exposure to the test item had been confirmed in blood and plasma samples taken in the range finder.

The animals dosed with MMC, the positive Control item, had statistically significant increases in the number of micronucleated cells compared with the concurrent Control group, which demonstrated that the test system was capable of detecting a known clastogen. There was a statistically significant decrease in the % RET in the positive Control group, indicating toxicity to the bone marrow.

Conclusion

There was no evidence of clastogenicity or aneugenicity following oral (gavage) administration of CGA226048 up to 2000 mg/kg/day in male mice. CGA226048 is considered to be neither clastogenic nor aneugenic in the mouse micronucleus test.

Micronucleus Data: Negative Control vs. Treated Groups

	Negative Control 0 mg/kg/day	CGA226048 500 mg/kg/day	CGA226048 1000 mg/kg/day	CGA226048 2000 mg/kg/day	MMC 1 mg/kg
N	6	6	6	6	5
Mean RET	19740.33	20230.17	20081.33	20356.67	20252.80

Mean MN-RET	45.50	48.83	44.50	44.50	415.40
Mean MN-RET frequency	0.23	0.24	0.22	0.22	2.01[WW]
Mean MN-RET frequency SD	0.06	0.02	0.05	0.07	0.79
Mean MN-RET frequency -SD	0.17	0.22	0.17	0.15	1.22
Mean MN-RET frequency +SD	0.29	0.26	0.27	0.29	2.80
Mean NCE	981208.17	1043746.67	853176.50	869982.33	5246793.60
Mean % RET	2.04	2.01	2.53	2.42	0.52[WW]
Mean % RET SD	0.37	0.51	0.79	0.55	0.36
Mean % RET -SD	1.67	1.50	1.74	1.87	0.16
Mean % RET +SD	2.41	2.52	3.32	2.97	0.88

MMC: mitomycin C
N: number of animals
WW: statistically significant (Wilcoxon's test) $p<0.01$
Note: any discrepancy in this table is due to rounding differences

Summary of Mouse Negative and Positive Control Data 2015

Males Negative Control							
	N	Mean	SD	95 % Control limit (mean +/- 2SD)		Range (min / max)	
MN-RET Frequency (MN-RET/RET)	45	0.20	0.05	0.09	0.30	0.13	0.33
% RET	45	1.80	0.57	0.65	2.95	1.16	3.32
Males Positive Control[1]							
	N	Mean	SD	95 % Control limit (mean +/- 2SD)		Range (min / max)	
MN-RET Frequency (MN-RET/RET)	30	2.65	0.77	1.10	4.19	1.06	4.24
% RET	30	0.68	1.20	-1.72	3.08	0.09	5.06

Note: any discrepancy in this table is due to rounding differences
Data was generated from individual animals
1: positive Control used was MMC 1 mg/kg administered by intraperitoneal injection
Whilst every effort has been made to ensure the accuracy of these data, they have not been audited by the QA unit.

Assessment and conclusion by applicant

Assessment:

The study was performed according to the 1997 version of OECD 474 and was compliant with the guideline that was in force at that time. However there are minor deficiencies in the study when it is compared to the current version of OECD 474 (2016). Only 2000 polychromatic erythrocytes (PCE) per dose level and control were analysed for micronuclei and different assay acceptance and evaluation criteria used compared to those recommended by OECD 474 (2016). The historical control data were not described according to the requirements of OECD 474 (2016). Overall, all the differences are considered to have not impacted the integrity or validity of the data generated. The study is scientifically valid.

The test is considered to meet the acceptance criteria as defined by OECD 474 (2016):

- OECD 474 2016 specifies clear requirements for demonstration of laboratory proficiency and maintenance of historical control data. For the current study the performing laboratory has a well-established record in performing the assay.
- HCD should be expressed as 95% (control limit, control interval), previously whole range. In the study report ranges and mean +/- SD are presented. This has no impact on the current study.
- OECD 474 2016 Data acceptance and evaluation criteria are specified and comparisons to historical control data are required for both control and treated cultures. For the current study the negative control response was close to the mean value of the negative control HCD, and the positive control response was similar to the mean positive control HCD response, additionally the positive control response was statistically significant. Hence, the study is fully acceptable.
- The concurrent vehicle control data are acceptable for addition to a historical control database.
- The concurrent positive controls induced a clear increase in micronucleated PCE compared with the concurrent vehicle control.
- OECD 474 2016: Requirement for proof of exposure of target tissue. In the current study bioanalytical data (qualitative determination in blood) are presented. These show the test substance to be systemically bioavailable.
- OECD 474 2016: 4000 PCE should be scored per animal in 5 animals for micronuclei and a 500 erythrocytes per animal assessed for determination of toxicity. In the 1997 version this was 2000

and 200 respectively. The test item was administered up to the MTD above which dose limiting toxicity was observed and systemic exposure was demonstrated by bioanalysis. In the current study 6 animals per treatment group were assessed for micronucleus formation in 2000 PCE per animal, in excess of the 1997 TG requirement. The Positive control gave a clear positive response, hence the sensitivity of the assay is demonstrated. An appropriate number of doses and cells has been analysed. Although <4000 PCE were examined per animal the data are consistently negative at 3 different dose levels. The reduced number of PCE examined per animals is considered to not have affected the sensitivity of the assay, additionally more animals per treatment group were used (six) than specified in the OECD TG (five).

- The criteria for the selection of highest dose are consistent with those described by OECD 474.
- OECD 474 2016: Test for statistical significance should be performed. Statistical analysis of the data was performed.
- OECD 474 2016: Trend test should be performed. A trend test was not performed on the data, however all treated groups had lower mean MN frequencies than the negative control group therefore a trend test would not provide any additional value to data interpretation.
- OECD 474 2016: Definition of "clear negative" and "clear positive" results. In the current study no increases in MN frequency were observed in treated groups, hence the criteria for study interpretation used in the report are satisfactory. Although no trend test was conducted the study may still be considered to be clearly negative.

Conclusion

The study complies with the data requirements given in Commission Regulation No 283/2013.

The test substance does not induce micronuclei in the bone marrow of orally treated mice.

Appendix 3 Exposure calculations

A 3.1 Operator exposure calculations (KCP 7.2.1.1)

A 3.1.1 Calculations for fludioxonil

Table A 13: Input parameters considered for the estimation of operator exposure

Formulation	A20607B
Active substance concentration	22.5 g/L
Type of seed	Sugar beet
Application rate	33.3 mL product / unit of seed (100 000 seeds/unit); equivalent to 0.75 g a.s. / unit of seed
Units treated	1500 units/day
Amount of a.s. handled	1.125 kg a.s./day
Dermal absorption	50%
Inhalation absorption	100%
Body weight	60 and 70 kg
AOEL	0.59 mg a.s./kg bw/day

Table A 14: Estimation of operator exposure towards fludioxonil - mixing/loading

Operator no.	2	5	7	12					
kg a.s. handled	60.8	60.8	182	211					
Seed-TROPEX Study results taken for extrapolation									
(all values in µg a.s. / kg a.s. and task)									
TADE	16.7	4.17	2.05	5.19					
IHL[1)]	0.161	0.088	0.032	0.123					
Extrapolation to fludioxonil in A20607B (amount a.s. handled = 1.125 kg/day)									
Route specific exposure - µg/person/day [2)]									
TADE	18.79	4.69	2.31	5.84					
IHL	0.181	0.099	0.036	0.138					
Route specific systemic exposure - µg/person/day [3)]									
TADE	9.395	2.345	1.155	2.92					
IHL	0.181	0.099	0.036	0.138					
Total systemic exposure - µg/person/day									
TADE & IHL	9.576	2.444	1.191	3.058					
Total systemic exposure - µg/kg bw/day for 60 kg body weight						arithm. mean	geom. mean	75th perc.	90th perc.
TADE & IHL	0.1596	0.0407	0.0199	0.051		0.0678	0.0507	0.0782	0.127
% of AOEL[4)]						0.01	0.01	0.01	0.02
Total systemic exposure - µg/kg bw/day for 70 kg body weight									
TADE & IHL	0.1368	0.0349	0.017	0.0437		0.0581	0.0434	0.067	0.109
% of AOEL[4)]						0.01	0.01	0.01	0.02

1) based on 16.7 l/min inhalation rate
2) µg a.s./kg a.s. and task determined in the study x 1.125 kg fludioxonil handled per day
3) Based on 50% dermal absorption and 100% inhalation absorption for fludioxonil
4) Total systemic exposure [µg/kg bw/day] /1000/ 0.59 x 100

Table A 15: Estimation of operator exposure towards fludioxonil - supervision/maintenance/cleaning of equipment

Operator no.	1	3	4	6	8	9	10	11				
kg a.s. handled	109	98	102	105	68	68	68	43				
Seed-TROPEX Study results taken for extrapolation												
(all values in µg a.s. / kg a.s. and task)												
TADE	16.4	11.3	10.2	9.6	63.4	28	77.9	161.7				
IHL[1)]	1.443	0.767	0.329	1.082	0.264	0.240	0.156	1.503				
Extrapolation to fludioxonil in A20607B (amount a.s. handled = 1.125 kg/day)												
Route specific exposure - µg/person/day [2)]												
TADE	18.45	12.71	11.48	10.8	71.33	31.5	87.64	181.91				
IHL	1.62	0.86	0.37	1.22	0.3	0.27	0.18	1.69				
Route specific systemic exposure - µg/person/day [3)]												
TADE	9.23	6.36	5.74	5.4	35.67	15.75	43.82	90.96				
IHL	1.62	0.86	0.37	1.22	0.3	0.27	0.18	1.69				
Total systemic exposure - µg/person/day												
TADE & IHL	10.85	7.22	6.11	6.62	35.97	16.02	44	92.65				
Total systemic exposure - µg/kg bw/day for 60 kg body weight									arithm. mean	geom. mean	75th perc.	90th perc.
TADE & IHL	0.181	0.12	0.102	0.11	0.6	0.267	0.733	1.544	0.457	0.286	0.633	0.976
% of AOEL[4)]									0.08	0.05	0.11	0.17
Total systemic exposure - µg/kg bw/day for 70 kg body weight												
TADE & IHL	0.155	0.103	0.087	0.095	0.514	0.229	0.629	1.324	0.392	0.245	0.543	0.838
% of AOEL[4)]									0.07	0.04	0.09	0.14

1) based on 16.7 l/min inhalation rate
2) µg a.s./kg a.s. and task determined in the study x 1.125 kg fludioxonil handled per day
3) Based on 50% dermal absorption and 100% inhalation absorption for fludioxonil
4) Total systemic exposure [µg/kg bw/day] /1000/ 0.59 x 100

A 3.1.2 Calculations for metalaxyl-M

Table A 16: Input parameters considered for the estimation of operator exposure

Formulation	A20607B
Active substance concentration	14.4 g/L
Type of seed	Sugar beet
Application rate	33.3 mL product / unit of seed (100 000 seeds/unit); equivalent to 0.48 g a.s. / unit of seed
Units treated	1500 units/day
Amount of a.s. handled	0.72 kg a.s./day
Dermal absorption	50%
Inhalation absorption	100%
Body weight	60 and 70 kg
AOEL	0.08 mg a.s./kg bw/day

Table A 17: Estimation of operator exposure towards metalaxyl-M - mixing/loading

Operator no.	2	5	7	12					
kg a.s. handled	60.8	60.8	182	211					
Seed-TROPEX Study results taken for extrapolation									
(all values in µg a.s. / kg a.s. and task)									
TADE	16.7	4.17	2.05	5.19					
IHL[1)]	0.161	0.088	0.032	0.123					
Extrapolation to metalaxyl-M in A20607B (amount a.s. handled = 0.72 kg/day)									
Route specific exposure - µg/person/day [2)]									
TADE	12.02	3	1.48	3.74					
IHL	0.116	0.063	0.023	0.089					
Route specific systemic exposure - µg/person/day [3)]									
TADE	6.01	1.5	0.74	1.87					
IHL	0.116	0.063	0.023	0.089					
Total systemic exposure - µg/person/day									
TADE & IHL	6.126	1.563	0.763	1.959					
Total systemic exposure - µg/kg bw/day for 60 kg body weight						arithm. mean	geom. mean	75th perc.	90th perc.
TADE & IHL	0.1021	0.0261	0.0127	0.0327		0.0434	0.0324	0.0501	0.081
% of AOEL[4)]						0.05	0.04	0.06	0.10
Total systemic exposure - µg/kg bw/day for 70 kg body weight									
TADE & IHL	0.0875	0.0223	0.0109	0.028		0.0372	0.0278	0.0429	0.07
% of AOEL[4)]						0.05	0.03	0.05	0.09

1) based on 16.7 l/min inhalation rate
2) µg a.s./kg a.s. and task determined in the study x 0.72 kg metalaxyl-M handled per day
3) Based on 50% dermal absorption and 100% inhalation absorption for metalaxyl-M
4) Total systemic exposure [µg/kg bw/day] /1000/ 0.08 x 100

Table A 18: Estimation of operator exposure towards metalaxyl-M - supervision/maintenance/cleaning of equipment

Operator no.	1	3	4	6	8	9	10	11				
kg a.s. handled	109	98	102	105	68	68	68	43				
Seed-TROPEX Study results taken for extrapolation												
(all values in µg a.s. / kg a.s. and task)												
TADE	16.4	11.3	10.2	9.6	63.4	28	77.9	161.7				
IHL [1)]	1.443	0.767	0.329	1.082	0.264	0.240	0.156	1.503				
Extrapolation to metalaxyl-M in A20607B (amount a.s. handled = 0.72 kg/day)												
Route specific exposure - µg/person/day [2)]												
TADE	11.81	8.14	7.34	6.91	45.65	20.16	56.09	116.42				
IHL	1.04	0.55	0.24	0.78	0.19	0.17	0.11	1.08				
Route specific systemic exposure - µg/person/day [3)]												
TADE	5.91	4.07	3.67	3.46	22.83	10.08	28.05	58.21				
IHL	1.04	0.55	0.24	0.78	0.19	0.17	0.11	1.08				
Total systemic exposure - µg/person/day												
TADE & IHL	6.95	4.62	3.91	4.24	23.02	10.25	28.16	59.29				
Total systemic exposure - µg/kg bw/day for 60 kg body weight									arithm. mean	geom. mean	75th perc.	90th perc.
TADE & IHL	0.116	0.077	0.065	0.071	0.384	0.171	0.469	0.988	0.293	0.183	0.405	0.625
% of AOEL [4)]									0.37	0.23	0.51	0.78
Total systemic exposure - µg/kg bw/day for 70 kg body weight												
TADE & IHL	0.099	0.066	0.056	0.061	0.329	0.146	0.402	0.847	0.251	0.157	0.347	0.536
% of AOEL [4)]									0.31	0.20	0.43	0.67

1) based on 16.7 l/min inhalation rate
2) µg a.s./kg a.s. and task determined in the study x 0.72 kg metalaxyl-M handled per day
3) Based on 50% dermal absorption and 100% inhalation absorption for sedaxane
4) Total systemic exposure [µg/kg bw/day] /1000/ 0.08 x 100

A 3.1.3 Calculations for sedaxane

Table A 19: Input parameters considered for the estimation of operator exposure

Formulation	A20607B
Active substance concentration	15 g/L
Type of seed	Sugar beet
Application rate	33.3 mL product / unit of seed (100 000 seeds/unit); equivalent to 0.5 g a.s. / unit of seed
Units treated	1500 units/day
Amount of a.s. handled	0.75 kg a.s./day
Dermal absorption	50%
Inhalation absorption	100%
Body weight	60 and 70 kg
AOEL	0.28 mg a.s./kg bw/day

Table A 20: Estimation of operator exposure towards sedaxane - mixing/loading

Operator no.	2	5	7	12					
kg a.s. handled	60.8	60.8	182	211					
Seed-TROPEX Study results taken for extrapolation									
(all values in µg a.s. / kg a.s. and task)									
TADE	16.7	4.17	2.05	5.19					
IHL [1)]	0.161	0.088	0.032	0.123					
Extrapolation to sedaxane in A20607B (amount a.s. handled = 0.75 kg/day)									
Route specific exposure - µg/person/day [2)]									
TADE	12.53	3.13	1.54	3.89					
IHL	0.121	0.066	0.024	0.092					
Route specific systemic exposure - µg/person/day [3)]									
TADE	6.265	1.565	0.77	1.945					
IHL	0.121	0.066	0.024	0.092					
Total systemic exposure - µg/person/day									
TADE & IHL	6.386	1.631	0.794	2.037					
Total systemic exposure - µg/kg bw/day for 60 kg body weight						arithm. mean	geom. mean	75th perc.	90th perc.
TADE & IHL	0.1064	0.0272	0.0132	0.034		0.0452	0.0338	0.0521	0.085
% of AOEL [4)]						0.02	0.01	0.02	0.03
Total systemic exposure - µg/kg bw/day for 70 kg body weight									
TADE & IHL	0.0912	0.0233	0.0113	0.0291		0.0387	0.0289	0.0446	0.073
% of AOEL [4)]						0.01	0.01	0.02	0.03

1) based on 16.7 l/min inhalation rate
2) µg a.s./kg a.s. and task determined in the study x 0.75 kg sedaxane handled per day
3) Based on 50% dermal absorption and 100% inhalation absorption for sedaxane
4) Total systemic exposure [µg/kg bw/day] /1000/ 0.28 x 100

Table A 21: Estimation of operator exposure towards sedaxane - supervision/maintenance/cleaning of equipment

Operator no.	1	3	4	6	8	9	10	11				
kg a.s. handled	109	98	102	105	68	68	68	43				
Seed-TROPEX Study results taken for extrapolation												
(all values in µg a.s. / kg a.s. and task)												
TADE	16.4	11.3	10.2	9.6	63.4	28	77.9	161.7				
IHL [1)]	1.443	0.767	0.329	1.082	0.264	0.240	0.156	1.503				
Extrapolation to sedaxane in A20607B (amount a.s. handled = 0.75 kg/day)												
Route specific exposure - µg/person/day [2)]												
TADE	12.3	8.48	7.65	7.2	47.55	21	58.43	121.28				
IHL	1.08	0.58	0.25	0.81	0.2	0.18	0.12	1.13				
Route specific systemic exposure - µg/person/day [3)]												
TADE	6.15	4.24	3.83	3.6	23.78	10.5	29.22	60.64				
IHL	1.08	0.58	0.25	0.81	0.2	0.18	0.12	1.13				
Total systemic exposure - µg/person/day												
TADE & IHL	7.23	4.82	4.08	4.41	23.98	10.68	29.34	61.77				
Total systemic exposure - µg/kg bw/day for 60 kg body weight									arithm. mean	geom. mean	75th perc.	90th perc.
TADE & IHL	0.121	0.08	0.068	0.074	0.4	0.178	0.489	1.03	0.305	0.191	0.422	0.651
% of AOEL [4)]									0.11	0.07	0.15	0.23
Total systemic exposure - µg/kg bw/day for 70 kg body weight												
TADE & IHL	0.103	0.069	0.058	0.063	0.343	0.153	0.419	0.882	0.261	0.163	0.362	0.558
% of AOEL [4)]									0.09	0.06	0.13	0.20

1) based on 16.7 l/min inhalation rate
2) µg a.s./kg a.s. and task determined in the study x 0.75 kg sedaxane handled per day
3) Based on 50% dermal absorption and 100% inhalation absorption for sedaxane
4) Total systemic exposure [µg/kg bw/day] /1000/ 0.28 x 100

A 3.2 Worker exposure calculations (KCP 7.2.3.1)

A 3.2.1 Calculations for fludioxonil

Table A 22: Input parameters considered for the estimation of worker exposure

Formulation	A20607B
Active substance concentration	22.5 g/L
Type of seed	Sugar beet
Application rate	33.3 mL product / unit of seed (100 000 seeds/unit); equivalent to 0.75 g a.s. / unit of seed
Sowing equipment	Precision seed drills
Dermal absorption	50%
Absorption by inhalation	100%
Body weight	60 and 70 kg
Sowing rate	1.3 units / ha
Area sown	20 ha / day
Amount of active substance applied	0.019 kg a.s./day
Indicative dermal exposure	1.28 mg a.s./kg a.s. handled/day
Indicative inhalation exposure	0.114 mg a.s./kg a.s. handled/day
AOEL	0.59 mg a.s./kg bw/day

Table A 23: Estimation of longer term worker exposure towards fludioxonil during loading and sowing of sugar beet seeds

Dermal exposure = mg a.s./kg a.s. handled/day × kg a.s. handled/day × % abs

= 1.28 × 0.019 × 50%

= 0.01216 mg a.s./day

Inhalation exposure = mg a.s./kg a.s. handled/day × kg a.s. handled/day × % abs

= 0.114 × 0.019 × 100%

= 0.002166 mg a.s./day

Total exposure (60 kg bw) = $\frac{\text{Dermal + inhalation}}{\text{kg bw}}$

= $\frac{0.01216 + 0.002166}{60}$

= **0.00024 mg a.s./kg bw/day**
= **0.04% AOEL**

Total exposure (70 kg bw) = $\frac{\text{Dermal + inhalation}}{\text{kg bw}}$

= $\frac{0.01216 + 0.002166}{70}$

= **0.00021 mg a.s./kg bw/day**

= **0.04% AOEL**

A 3.2.2 Calculations for metalaxyl-M

Table A 24: Input parameters considered for the estimation of worker exposure

Formulation	A20607B
Active substance concentration	14.4 g/L
Type of seed	Sugar beet
Application rate	33.3 mL product / unit of seed (100 000 seeds/unit); equivalent to 0.48 g a.s. / unit of seed
Sowing equipment	Precision seed drills
Dermal absorption	50%
Absorption by inhalation	100%
Body weight	60 and 70 kg
Sowing rate	1.3 units / ha
Area sown	20 ha / day
Amount of active substance applied	0.012 kg a.s./day
Indicative dermal exposure	1.28 mg a.s./kg a.s. handled/day
Indicative inhalation exposure	0.114 mg a.s./kg a.s. handled/day
AOEL	0.08 mg a.s./kg bw/day

Table A 25: Estimation of longer term worker exposure towards metalaxyl-M during loading and sowing of sugar beet seeds

Dermal exposure = mg a.s./kg a.s. handled/day × kg a.s. handled/day × % abs

= 1.28 × 0.012 × 50%

= 0.00768 mg a.s./day

Inhalation exposure = mg a.s./kg a.s. handled/day × kg a.s. handled/day × % abs

= 0.114 × 0.012 × 100%

= 0.001368 mg a.s./day

Total exposure (60 kg bw) = $\frac{\text{Dermal + inhalation}}{\text{kg bw}}$

= $\frac{0.00768 + 0.001368}{60}$

= **0.00016 mg a.s./kg bw/day**
= **0.19% AOEL**

Total exposure (70 kg bw) = $\frac{\text{Dermal + inhalation}}{\text{kg bw}}$

= $\frac{0.00768 + 0.001368}{70}$

= **0.00013 mg a.s./kg bw/day**
= **0.17% AOEL**

A 3.2.3 Calculations for sedaxane

Table A 26: Input parameters considered for the estimation of worker exposure

Formulation	A20607B
Active substance concentration	15 g/L
Type of seed	Sugar beet
Application rate	33.3 mL product / unit of seed (100 000 seeds/unit); equivalent to 0.5 g a.s. / unit of seed
Sowing equipment	Precision seed drills
Dermal absorption	50%
Absorption by inhalation	100%
Body weight	60 and 70 kg
Sowing rate	1.3 units / ha
Area sown	20 ha / day
Amount of active substance applied	0.013 kg a.s./day
Indicative dermal exposure	1.28 mg a.s./kg a.s. handled/day
Indicative inhalation exposure	0.114 mg a.s./kg a.s. handled/day
AOEL	0.28 mg a.s./kg bw/day

Table A 27: Estimation of longer term worker exposure towards sedaxane during loading and sowing of sugar beet seeds

Dermal exposure = mg a.s./kg a.s. handled/day × kg a.s. handled/day × % abs

= 1.28 × 0.013 × 50%

= 0.00832 mg a.s./day

Inhalation exposure = mg a.s./kg a.s. handled/day × kg a.s. handled/day × % abs

= 0.114 × 0.013 × 100%

= 0.001482 mg a.s./day

Total exposure (60 kg bw) = $\frac{\text{Dermal + inhalation}}{\text{kg bw}}$

= $\frac{0.00832 + 0.001482}{60}$

= **0.00016 mg a.s./kg bw/day**
= **0.06% AOEL**

Total exposure (70 kg bw) = $\frac{\text{Dermal + inhalation}}{\text{kg bw}}$

= $\frac{0.00832 + 0.001482}{70}$

= **0.00014 mg a.s./kg bw/day**
= **0.05% AOEL**

A 3.3 Resident and bystander exposure calculations (KCP 7.2.2.1)

Resident and bystander exposure not applicable for seed treatment products.

Appendix 4 Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

Report:	KCP 7.2.1.1 [redacted] (2006) Determination of operator exposure to imidacloprid during treatment of sugar beet seeds with IMPRIMO® in France. Amended Final Report 04B033 HI, Rhodia Recherches et Technologies, Laboratoire d'Hygiène Industrielle, F-69162 Saint-Fons Cedex, France. Unpublished. The data are property of the SeedTROPEX Group. Syngenta File No. ASF654/0001

Guidelines

OECD Series on Principles of GLP and Compliance Monitoring No. 1 (as revised in 1997) "OECD Principles on Good Laboratory Practice", Paris 1998.

OECD Series on Principles of GLP and Compliance Monitoring No. 6 (revised)" The application of GLP-Principles to Field Studies", Paris 1999.

OECD Series on Principles of GLP and Compliance Monitoring No. 13" The application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies 2002."

Quality Assurance: OECD Series on Principles of GLP and Compliance Monitoring No. 4 (revised) "Quality Assurance and GLP", Paris 1999.

GLP

Yes (certified laboratory)

Executive Summary

The study was conducted in France in 2004 in two seed treatment plants specially equipped for treatment of sugar beet seeds. The two main application techniques used in sugar beet seed treatment plants were investigated during this study i.e. batch treatment with seed coating and drying operated under negative pressure and coating and drying in fluid bed equipment.

Operators involved in the study were employees of these seed treatment plants. In total 12 replicates (6 per site) were monitored (4 during mixing/loading and 8 during seed treatment operations including supervision, maintenance and cleaning of the equipment). All operators were monitored for a period of a usual working shift.

Potential and actual dermal exposure to imidacloprid was measured by means of whole-body passive dosimetry. The outer dosimeter clothing (long work trousers, long-sleeved shirt and work jacket) corresponded to what workers usually wear at the particular period when sugar beet seeds are treated. Operators also wore a Tyvek® coverall over outer dosimeter clothing following the working rules of the plant. The inner dosimeters (representing the skin) consisted of long-sleeved and long-legged cotton undergarments. Head exposure was measured by performing face/neck wipes, potential and actual hand exposure was determined by performing hand and glove washes. Potential inhalation exposure was measured by means of personal air sampling pumps and an IOM sampler which was positioned in the breathing zone of the operators.

All dosimeter specimens were analysed for imidacloprid.

Materials

Test Item:	IMPRIMO® (containing 400 g/L imidacloprid and 17.8 g/L tefluthrin)
Description:	Water-based seed dressing liquid, formulated as a flowable concentrate (FS)

Lot/Batch #:	Various (commercial product)
Purity:	400 g/L imidacloprid, 17.8 g/L tefluthrin (nominal contents)
Stability of test compound:	Commercial product within shelf-life

Study parameters

Application rate:	0.225 L product/unit seed, corresponding to 90 g imidacloprid and 4.0 g tefluthrin per unit (1 unit seeds = 100'000 seeds).
Seed treatment equipment:	Drum treater under negative pressure (Mereville); fluidized bed treaters (Nerac).
Monitoring times:	Mixing/loading: 78 – 97 minutes (average: 88 minutes); Seed treatment / maintenance / cleaning: 270 – 437 minutes (average: 379 minutes).
Amount seed treated:	482 – 1218 units (average: 921 units).
Amount product used:	Mixing/loading: 181 – 627 kg (average: 383 kg); Seed treatment / maintenance / cleaning: 129 – 325 kg (average: 246 kg)
Number of replicates:	Mixing/loading: 4 (2 in Mereville and 2 in Nerac); Seed treatment / maintenance / cleaning: 8 (4 in Mereville and 4 in Nerac).

Description of mixing / loading

The product was supplied in 25 litre containers.

At Mereville, the mixing/loading operation was performed in a specific area at the opposite side of the seed treatment area. The task consisted in manually loading the components of the mixture containing IMPRIMO® into a vessel for around 30 minutes, stirring the mixture for around 45 minutes and then gravity transferring the mixture into a 1000 L container.

At Nerac, the mixing/loading operation was performed in a specific area closed to the seed treatment area. IMPRIMO® was pumped directly into a storage container using a plunger, which was manually transferred from one container to the other one. For that purpose, all the containers were first opened. IMPRIMO® was pumped. Containers were rinsed with water one by one. Rinsing water was then transferred into the vessel used for mixture preparation. After that, IMPRIMO® containers were re-plugged.

Description of seed treatment activities (supervision, maintenance, cleaning)

At Mereville one operator per shift conducted treatment operations. Coating was performed in two drums which ran in parallel. Around 300 units of seeds were treated per batch in each drum. Coating of each batch lasted around 2 hours. A cleaning cycle was conducted after two treatment cycles. Cleaning was partially automated. The drum was automatically washed with water, however, operators needed to finish drum cleaning using high-pressure water. They also had to unload unused mixture and manually clean the discharge hopper and filters. Some parts of the equipment were removed and washed in a sink.

At Nerac, two operators per shift conducted the seed treatment. Coating was simultaneously performed in 10 fluidized bed treaters. Per batch, 10 units of seeds were treated in each fluidized bed system. At the end of a coating cycle, either a new cycle or a cleaning cycle began. Cleaning was done manually with water and a sponge. Some parts of the equipment were removed and washed in a sink.

Summarised study results

Table A 28: Operator exposure to imidacloprid during mixing/loading

	OP 02	OP 05	OP 07	OP 12	arithm. mean	geom. mean	70th perc.	90th perc.
Total potential dermal exposure (TPDE) 1)								
µg a.s./task	234940	24207	85917	192216	134320	98445	196488	222123
Total actual dermal exposure (TADE) 2)								
µg a.s./task	1013	254	373	1095	684	569	1021	1070
µL IMPRIMO/task	2.53	0.634	0.933	2.74	1.71	1.42	2.55	2.68
µg a.s./hr	627	164	270	842	476	391	648	777
µg a.s./kg b.w. & task	12.1	3.02	4.97	13.5	8.39	7.03	12.2	13.1
µg a.s./kg a.s. & task	16.7	4.17	2.05	5.19	7.02	5.22	6.34	13.2
Potential inhalation exposure (IHL) 3)								
µg a.s./task	8.23	4.51	4.84	21.8	9.84	7.91	9.59	17.7
µL IMPRIMO/task	0.021	0.011	0.012	0.054	0.025	0.020	0.024	0.044
µg a.s./hr	5.09	2.91	3.50	16.7	7.06	5.43	6.25	13.2
µg a.s./kg b.w. & task	0.098	0.054	0.065	0.269	0.121	0.098	0.115	0.217
µg a.s./kg a.s. & task	0.135	0.074	0.027	0.103	0.085	0.072	0.106	0.126

1) Sum of residues on outer dosimeters (work trousers and work jacket, shirt, Tyvek® coverall where worn), inner dosimeters (representing the skin), face/neck wipes, hand wash solutions, gloves. Values for individual operators have been taken from Table 13 of the Amended Final Report.
2) Sum of residues on inner dosimeters (representing the skin), face/neck wipes, hand wash solutions.
3) Based on an average ventilation rate of 14 L/min.

Table A 29: Operator exposure to imidacloprid during seed treatment (supervision / maintenance / cleaning)

	OP 01	OP 03	OP 04	OP 06	OP 08	OP 09	OP 10	OP 11	arith m. mean	geom. mean.	70th perc.	90th perc.
	Total potential dermal exposure (TPDE) 1)											
µg a.s./task	128027	137653	31594	20252	74322	39043	54903	59059	68107	56651	72796	130915
	Total actual dermal exposure (TADE) 2)											
µg a.s./task	1794	1110	1046	1014	4283	1890	5266	7022	2928	2239	4044	5793
µg a.s./hr	246	173	152	153	695	304	829	1561	514	358	656	1049
µg a.s./kg b.w. & task	32.6	13.7	19.0	12.5	57.1	22.4	53.5	86.7	37.2	29.8	51.4	66.0
µg a.s./kg a.s. & task	16.4	11.3	10.2	9.60	63.4	28.0	77.9	161.7	47.3	28.3	59.9	103
	Potential inhalation exposure (IHL) 3)											
µg a.s./task	132	63.1	28.2	95.5	14.9	13.6	8.82	54.6	51.3	34.9	62.3	106
µg a.s./hr	18.1	9.8	4.08	14.4	2.42	1.93	1.26	12.1	8.02	5.42	11.9	15.5
µg a.s./kg b.w. & task	2.39	0.779	0.512	1.18	0.199	0.161	0.090	0.674	0.748	0.465	0.769	1.54
µg a.s./kg a.s. & task	1.21	0.643	0.276	0.907	0.221	0.201	0.131	1.26	0.605	0.440	0.881	1.22

1) Sum of residues on outer dosimeters (work trousers and work jacket, shirt, Tyvek® coverall where worn), inner dosimeters (representing the skin), face/neck wipes, hand wash solutions, gloves. Values for individual operators were taken from Table 14 of the Amended Final Report.
2) Sum of residues on inner dosimeters (representing the skin), face/neck wipes, hand wash solutions.
3) Based on an average ventilation rate of 14 L/min.

Conclusions

The study is considered to provide suitable data for the estimation of operator exposure during treatment of sugar beet seeds by means of drum coaters and fluidized bed treaters.

([redacted] 2006)

Report:	KCP 7.2.3.1 [redacted] (2007) Determination of operator exposure to imidacloprid during loading/sowing of GAUCHO® treated maize seeds under realistic field conditions in Germany and Italy. Amendment No 1 to Final Report. SGS Institut Fresenius, Im Maisel 14, D-65232 Taunusstein. Study No. IF-05/00328969; 25 October 2007. Unpublished. The data are property of the SeedTROPEX Group. Syngenta file No. ASF654/0002

Guidelines

OECD Series on Testing and Assessment No. 9 "Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application", Paris 1997. OCDE/GD(97)148.

There were no deviations from the guideline which were considered to compromise the scientific validity of the study.

GLP

Yes (certified laboratory)

Executive Summary

The purpose of the study was to determine potential and actual dermal exposure as well as potential inhalation exposure of operators to imidacloprid during loading and sowing of treated maize seeds under realistic conditions and using typical agricultural equipment.

In total 16 operators were monitored, four in Italy, three in Bavaria, four in Saxony-Anhalt and Brandenburg, and five in the Emsland and Münster region. The farms were selected in order to cover different types of pneumatic sowing machines and different local practices of maize sowing. Therefore the data of the study cover a broad range of sowing aspects and can be considered as representative for maize sowing in Western Europe. All seeds were commercial brands and purchased by the farmers from the local market. The results of 15 operators were taken into account for the exposure calculations. The results of one operator were excluded due to an extremely low amount of imidacloprid (2% of the nominal content) detected on the seeds handled.

The exposure to imidacloprid was measured by means of whole-body passive dosimetry. Head exposure was measured by performing face/neck wipes. Exposure of the hands was determined by a hand wash procedure. Potential inhalation exposure was measured by means of personal air sampling pumps and an IOM sampler which was positioned in the breathing zone of the operators.

Two phases of maize sowing were monitored: the loading of seed hoppers and the sowing phase. Exposure of the hands and *via* inhalation was determined separately for the activities of loading and sowing the seed, exposure of the body was determined for the combined activity. All dosimeter specimens were analysed for imidacloprid.

Materials and study parameters

Test Item:	Commercial maize seed treated with imidacloprid containing seed treatment products, i.e. “Gaucho FS 600” or “Gaucho FS 350”.
Active substance:	Imidacloprid.
Nominal application rate:	1.0 and 1.2 mg imidacloprid/kernel for seeds treated in Germany and Italy, respectively.
Number of replicates:	16, of these 15 were considered for the exposure calculations.
Sowing equipment:	Pneumatic drillers of various manufacturers, with working widths ranging from 3 to 9 metres.
Areas sown:	5.5 to 40.2 ha (average 14.3).
Amounts a.s. handled:	0.644 to 3.544 kg (average 1.327 kg).
Total working times:	307 to 492 minutes (average 424 min).

Study results

Exposure was expressed as mg per operator and day, mg per operator and kg a.s. handled and mg per operator and hour. The results are summarised below.

Table A 30: Summarised results of the SeedTROPEX study on loading/sowing maize seeds

Operator Code	PDE	ADE	PIE	a.s. handled	nPDE	nADE	nPIE	working time	nPDE	nADE	nPIE
	mg/op.	mg/op.	mg/op.	kg	mg/kg a.s.	mg/kg a.s.	mg/kg a.s.	minutes	mg/hr	mg/hr	mg/hr
OA	8.915	0.651	0.0511	0.6863	12.99	0.949	0.0744	360	1.486	0.109	0.0085
OB	13.33	1.420	0.0726	0.8223	16.21	1.726	0.0883	472	1.695	0.180	0.0092
OC	59.08	2.779	0.2267	0.6788	87.05	4.094	0.3340	407	8.710	0.410	0.0334
OR	9.957	0.939	0.0591	0.644	15.46	1.458	0.0918	307	1.946	0.184	0.0115
OE	5.997	0.319	0.0764	3.544	1.692	0.090	0.0215	434	0.829	0.044	0.0106
OF	1.975	0.082	0.0246	1.26	1.568	0.065	0.0195	427 1)	0.278	0.011	0.0035
OH	4.531	0.217	0.0634	1.862	2.433	0.116	0.0341	404	0.673	0.032	0.0094
OJ	2.073	0.194	0.0223	0.91	2.278	0.213	0.0245	437	0.285	0.027	0.0031
OK	3.792	1.027	0.0256	1.337	2.837	0.768	0.0191	492	0.464	0.126	0.0031
OM	2.409	0.722	0.1701	1.4	1.721	0.516	0.1215	485	0.298	0.089	0.0210
OL	15.08	7.220	0.1949	1.842	8.189	3.921	0.1058	421	2.149	1.029	0.0278
ON	0.938	0.101	0.0323	1.16	0.847	0.087	0.0278	403	0.146	0.015	0.0048
OO	1.881	1.009	0.0295	1.49	1.263	0.677	0.0198	466	0.242	0.130	0.0038
OP	14.96	0.497	0.1079	0.865	17.29	0.574	0.1248	406	2.210	0.073	0.0159
OQ	8.045	0.415	0.2673	1.404	5.730	0.296	0.1904	435	1.110	0.057	0.0369
Arithm. mean	10.20	1.173	0.0949	1.327	11.84	1.037	0.0865	424	1.501	0.168	0.0135
Geom. mean	5.73	0.582	0.0680	1.190	4.821	0.489	0.0572	421	0.817	0.083	0.0097
75th perc.	11.64	1.018	0.1390	1.447	14.23	1.204	0.1137	452	1.820	0.155	0.0185
90th perc.	15.03	2.235	0.2389	1.854	16.86	3.043	0.1642	480	2.186	0.319	0.0312
Min.	0.983	0.082	0.0223	0.644	0.847	0.065	0.0191	307	0.146	0.012	0.0031
Max.	59.08	7.220	0.2673	3.544	87.05	4.094	0.3340	492	8.710	1.029	0.0369

PDE (Potential Dermal Exposure) = Sum of residues on outer clothing (coverall as work wear & shirt worn underneath), inner dosimeter representing the skin, face/neck wipes, protective gloves and handwash solutions.
ADE (Actual Dermal Exposure) = sum of residues on inner dosimeter representing the skin, face/neck wipes and hand wash solutions.
PIE (Potential Inhalation Exposure) is based on an average ventilation rate of 20.84 L/min
nPDE = normalised Potential Dermal Exposure
nADE = normalised Actual Dermal Exposure
nPIE = normalised Potential Inhalation Exposure
1) 407 in Table 5 of the Amendment No. 1 to the Report (typographical error)

Table A 31: Derivation of empirical and parametric 75th percentiles for actual dermal exposure and potential inhalation exposure using the SeedTROPEX study on loading/sowing maize seeds

	Actual Dermal exposure	**Potential inhalation exposure**
EMPIRICAL STATISTICS	**(mg a.s./ kg a.s. applied)**	**(mg a.s./ kg a.s. applied)**
number	15	15
minimum	0.065	0.019202571
geometric mean	0.489172095	0.057212691
average	1.036666667	0.08653345
75 percentile	1.204	**0.114**
maximum	4.094	0.334035429

TEST FOR LOGNORMALITY		
Number	15	15
R square LN vs n order	0.966199807	0.913920761
r	0.982954631	0.95599203
Filliben critical value	0.939	0.939
Ho y is from normal distribution	accept	accept
LOGNORMAL PARAMETERS		
Number	15	15
mean (LN)	-0.715	-2.861
sd (LN)	1.345	0.946
one-tailed t values		
$t_{n-1, 0.75}$	0.69241707	0.69241707
PARAMETRIC CENTILES		
75th centile	**1.280**	0.113

75th percentile values in bold are used in risk assessment. The agreed selection rule in the EFSA Guidance on Pesticides Exposure Assessment of Operators, Workers, Residents and Bystanders considers the higher value of the sample and the percentile estimate as long as this value is below the sample maximum. Otherwise, the sample maximum should be chosen. (EFSA Journal 2014;12(10):3874)

Conclusions

The study is considered to provide suitable data for the estimation of operator exposure during loading and sowing of treated seeds by means of pneumatic drillers in Western Europe.

([redacted] 2007)